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US High Production Volume Chemical Program

Category Summary

For

Crude Butadiene C4 Category

Prepared by:

Olefins Panel of the American Chemistry Council

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EXECUTIVE SUMMARY

The Olefins Panel of the American Chemistry Council (ACC) hereby submits the category summary report for the Crude Butadiene C4 Category under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program (Program). The purpose of this report is to:

- Present results of an assessment to determine whether four production streams can be adequately characterized with existing data and additional data as described in the Crude Butadiene C4 Category test plan.
- Summarize the SIDS (Screening Information Data Set) physicochemical, environmental fate and effects, and human health HPV Program endpoints for the Crude Butadiene C4 Category.
- Provide a description of manufacturing processes, potential exposure sources, and uses for Crude Butadiene C4 streams.

The Crude Butadiene C4 Category originally contained four streams. After all data were evaluated to determine whether the streams formed a cohesive category, it was decided that two streams, Pyrolysis C3+ and Pyrolysis C4+, should be considered a separate category based on composition and effects of stream constituents, which are not shared by all four streams. Therefore, these two streams were removed from this category. A category summary report characterizing their HPV Program endpoints will be prepared and submitted separately. Consequently, the following category report summarizes HPV Program data for the C4 Crude Butadiene and Butadiene Unit Heavy Ends streams, which constitute the revised Crude Butadiene C4 Category.

The two streams retained in the Crude Butadiene C4 Category consist of a complex mixture of hydrocarbons. The typical carbon (C) number distribution for these streams ranges predominantly between C3 and C5. Much of the data used to characterize this category are from 1,3-butadiene, which is the most chemically reactive of the constituents and hence presumed the most biologically active component and major contributor to toxicological activity. This chemical is present in the two streams covered by this category at concentrations between approximately 10 to 92% (by weight).

Exposure

Industrial emissions of chemicals such as 1,3-butadiene are reported annually to the EPA and made available to the public in the Toxics Release Inventory (TRI). The TRI data indicate that industrial emissions of 1,3-butadiene have declined by 69% since 1988 or from 7.7 million pounds to 2.4 million pounds per year in 2000.

Fugitive emissions and other emission sources can result in the potential for low-level ambient air concentrations of constituents from the two streams at locations neighboring industrial facilities where they are manufactured. Both EPA and state agencies enforce a wide range of volatile organic compound and hazardous air pollutant environmental regulations that control these emissions. 1,3-Butadiene off-property concentrations from category streams will be further reviewed nationally by EPA as the Clean Air Act Section 112f residual risk provisions are implemented. These regulations on 1,3-butadiene emissions limit the potential for emissions of the streams in this HPV Category.

Human Health

Crude Butadiene C4 streams have a low order of acute toxicity. The components of Crude Butadiene C4 streams are gaseous at normal temperature and pressure; thus, ingestion or dermal absorption of this material is unlikely. Minimal effects were observed at concentrations of 5,300 mg/m^3.

Liquid Crude Butadiene C4 (test material was cooled in a dry ice bath) did not produce dermal or ocular irritation in rabbits. Exposure to liquid crude butadiene C4 is unlikely, as the components of

the streams in this category are gases at normal temperature and pressure.

A species difference in repeated dose toxicity of crude butadiene C4 was apparent between rats and mice. Minimal effects were reported in rat repeated dose toxicity tests exposed to several Crude Butadiene C4 streams (1,3-butadiene content ranging from 10 to 99.2%). The no observable adverse effect levels were the highest concentrations tested or 17,679; 20,000; or 25,100 mg/m^3 (8,000; 9,060; or 11,365 ppm, respectively) following 90, 36, or 9 days of exposure, respectively. In contrast, mortality was observed in mice exposed to 2,761 mg/m^3 1,3-butadiene (99.2%) for 90 days. Well documented species differences in 1,3-butadiene metabolism are the likely reason for the noted differences in repeat dose toxicity. Mice produce greater amounts of toxic metabolites following 1,3-butadiene exposure than rats. Available data suggest humans metabolize 1,3-butadiene similarly to rats.

Test data demonstrate that crude butadiene C4 can produce genotoxicity. *In vitro*, crude butadiene C4 demonstrated little activity in reverse mutation assays conducted in *Salmonella typhimurium* either in the presence or absence of metabolic activation. In addition, crude butadiene C4 did not increase the number of transformed foci in C3H/10T1/2 cloned 8 mouse embryo fibroblast cells. In the mouse lymphoma assay, evidence of mutagenic activity in mouse lymphoma L5178Y cells in culture was observed in the absence of metabolic activation, but not in the presence of metabolic activation. *In vivo*, several crude butadiene streams, containing 10 to 45% 1,3-butadiene, induced micronuclei formation in rats and mice following inhalation exposure.

No reproductive or developmental toxicity was observed in rats exposed to crude butadiene during the conduct of an OECD 422 repeat dose reproductive/developmental toxicity screen. Exposures to concentrations of 20,000 mg/m^3 were without effect. Further, in a prenatal developmental toxicity study, inhalation exposure of pregnant rats to 1,3-butadiene on days 5 to 16 (inclusive) of gestation elicited no developmental toxicity at any tested concentration up to 2,210 mg/m^3. Maternal toxicity was observed at levels of 442 mg/m^3. Similar to observations of species differences in repeat dose toxicity, mice were more sensitive than rats in developmental and reproductive toxicity following exposure to 1,3-butadiene. This increased sensitivity was apparent in effects on male germ cells observed in a dominant lethal study and an assessment of sperm morphology in male mice and fetal effects observed in a prenatal developmental toxicity study.

Environment

Results of distribution modeling show that chemical constituents of streams in the Crude Butadiene C4 Category will partition primarily to the air compartment, with a negligible amount partitioning to water. In the air, these constituents have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals. This is expected to be the dominant route of loss and degradation process for constituents of these streams. Aqueous photolysis and hydrolysis will not contribute to the transformation of category constituents in aquatic environments because they are either poorly or not susceptible to these reactions.

Although the biodegradability of streams in this category has not been evaluated with standard testing procedures because of their high volatility, studies have demonstrated that several category constituents can be degraded by bacteria isolated from soil and surface water samples. The results from these studies show that selected stream constituents are subject to microbial degradation. However, biodegradation is unlikely to contribute to the overall degradation of constituents from these streams because they tend to partition to the air compartment.

Due to the fact that streams in this category are gaseous at ambient temperature and pressure and expected to partition predominantly to the atmosphere, aquatic toxicity testing was not conducted. However, aquatic toxicity was assessed with a model that is based on an equation developed for neutral organic chemicals, which is a reliable estimation method for the class of chemicals in streams from this category. Calculated toxicity values for two to four day exposures suggest that

category members have the potential to produce moderate toxicity, based on an effect range of 15.35 to 40.27 mg/L for selected stream constituents.

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* Companies that are part of the Olefins Panel, but do not produce Chemical Abstracts Service registration numbers in the Crude Butadiene C4 Category.

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1 CATEGORY DESCRIPTION AND JUSTIFICATION

1.1 Category Identification

For purposes of the U.S. High Production Volume (HPV) Chemical Challenge Program (Program), the Crude Butadiene C4 Category test plan submitted in May 2000 (Olefins Panel, HPV Implementation Task Group, 2000) included four production streams and eleven Chemical Abstracts Service (CAS) registration numbers (RNs) (Table 1). The test plan identified existing data and additional data to be developed, based on an extensive technical review of the category, to adequately characterize the four streams for the HPV Program endpoints. After the additional data were developed and all data evaluated to determine whether the streams formed a cohesive category as originally envisaged, it was decided that two streams, Pyrolysis C3+ and Pyrolysis C4+, should be considered as a separate category based on compositional differences and potential effects of stream constituents not shared by all four streams. Therefore, a category summary report that characterizes the HPV Program endpoints will be prepared and submitted separately for these two streams.

The following category report summarizes HPV Program data for the C4 Crude Butadiene and Butadiene Unit Heavy Ends streams, which constitute the revised Crude Butadiene C4 Category and contain ten CAS RNs (the CAS RNs listed in Table 1 except CAS RN 68513-68-8, which was shared exclusively by the Pyrolysis C3+ and Pyrolysis C4+ streams; a second CAS RN, 64742-83-2, is also shared by the C4 Crude Butadiene stream and will be retained in the revised category).

Table 1. Production Streams, CAS RNs, and CAS RN Names in the Crude Butadiene C4 Category

Production Streams	CAS RN	CAS RN Name
C4 Crude Butadiene	68476-52-8	Hydrocarbons, C4, Ethylene-Manuf.-By-Product
	68187-60-0	Hydrocarbons, C4, Ethane-Propane-Cracked
	68955-28-2	Gases, (Petroleum), Light Steam-Cracked, Butadiene Conc.
	64742-83-2	Naphtha, (Petroleum), Light Steam Cracked
	68476-44-8	Hydrocarbons, >C3
	68956-54-7	Hydrocarbons, C4, Unsatd.
	68477-41-8	Gases, Petroleum, Extractive, C3-5, Butadiene-Butene-Rich
	25167-67-3	Butene
Butadiene Unit Heavy Ends	69103-05-5	Hydrocarbons, C4-7, Butadiene Manuf. By-Product
	68477-41-8	Gases, Petroleum, Extractive, C3-5, Butadiene-Butene-Rich
	68512-91-4	Hydrocarbons, C3-4-Rich, Petroleum Distillates
Pyrolysis C3+	64742-83-2	Naphtha, (Petroleum), Light Steam Cracked
	68513-68-8	Residues, (Petroleum), Deethanizer Tower
Pyrolysis C4+	64742-83-2	Naphtha, (Petroleum), Light Steam Cracked

Note: The CAS numbers associated with corresponding production streams are shown in the above table. The definitions found in the TSCA Chemical Substance Inventory for the CAS RNs in this category are vague with respect to composition. Therefore, it is not uncommon to find that one CAS RN is used to describe different streams (different compositions) or that two or more CAS RNs are used to describe one stream (similar composition). Pyrolysis C3+ and Pyrolysis C4+, originally included in the C4 Crude Butadiene Category, will be considered as a separate category based on compositional and other differences.

The two commercial production streams, C4 Crude Butadiene and Butadiene Unit Heavy Ends, are similar from a process and toxicology perspective. Each stream can vary in composition, not only between manufacturers but also for an individual manufacturer, depending on feedstock type and process operating conditions. Although the chemical composition of the streams can vary, the defining characteristic of the two streams is that each contains a mixture of chemicals from a reaction or separation activity in the Olefins Industry hydrocarbon processes and each contains 1,3-butadiene at a minimum concentration of approximately 10%.

The two streams in this category are composed of a complex mixture of hydrocarbons. The typical carbon (C) number distribution for these streams ranges predominantly between C3 and C5. The major stream in the category on a production volume basis is a C4 stream that contains between approximately 10 to 82% 1,3-butadiene and is referred to as "C4 Crude Butadiene". Both streams contain significant levels of C4 olefins and 1,3-butadiene in particular, which is the most biologically active constituent and the major contributor to toxicological activity. This commonality is the basis for considering the two streams as a category for purposes of the HPV Program.

The TSCA Chemical Substance Inventory definitions for the CAS RNs in this and in other categories from the Olefins Panel's HPV Program can be vague with respect to composition. Therefore, it is not uncommon that a CAS RN is correctly used to describe different streams (different compositions) or that two or more CAS RNs are used to describe one stream (similar composition or process). For this reason, the data matrix for this category was developed based on two compositionally differentiated process streams, rather than on the CAS RNs in this category.

The Crude Butadiene C4 Category streams arise from production processes associated with ethylene manufacturing (see Appendix I for a description of the ethylene and associated processes). The category stream names have changed since the test plan for this category was prepared in 2001. The change came as a result of a review and a decision by the Olefins Panel to use terminology that is more broadly applied throughout the industry. Briefly, the two process streams are:

(1) C4 Crude Butadiene stream is produced from the distillation of a liquefied portion cracked gas. This stream typically contains approximately 40 to 60% 1,3-butadiene (Table 2). However, it can contain as little as 10% or as much as 82% 1,3-butadiene. Other hydrocarbons in this stream are predominately C4. This stream was referred to as Butadiene Concentrate in the Crude Butadiene C4 Category Test Plan (Olefins Panel, HPV Implementation Task Group, 2001).

(2) Butadiene Unit Heavy Ends stream is produced from extractive distillation. This stream contains approximately 13 to 92% 1,3-butadiene (Table 2). Other hydrocarbons in this stream are predominately C4. This stream was referred to as High Butadiene Heavy Ends in the Crude Butadiene C4 Category Test Plan.

Table 2. Typical Constituent (wt%) Range in Streams of the Crude Butadiene C4 Category

Constituent	C4 Crude Butadiene Stream (wt %)	Butadiene Unit Heavy Ends Stream (wt %)
tert-Butyl Catechol	0 - 0.01	
Methanol	0.0 - 0.3	
Methylacetylene & Propadiene	0.0 - 2.3	
Ethyl- & Vinylacetylene	0.7 - 3.0	
Propylene	0.0 - 1.9	
Other C3 & Lighter Hydrocarbons	0.5 - 1.7	
Isobutane	0.4 - 22	
Isobutylene	0.5 - 29	
n-Butane	1.5 - 30	0.0 - 6.0
cis- & trans-Butene-2	3.5 - 54	5 - 50
Butene-1	2.5 - 25	0.0 - 4.0
1,3-Butadiene	10 - 82	13 - 92
1,2-Butadiene	0.0 - 1.4	0.0 - 2.0
Other C5 & Higher	0.0 - 8.0	
Vinylcyclohexene	0.0 - 1.0	
Isopentane		0.0 - 3.0
Other C8 Hydrocarbons		0.0 - 4.0

Note 1: The balance of these streams is expected to be other hydrocarbons that have boiling points in the ranges of the listed constituents.

Note 2: The ranges should not be considered to represent absolute limits for these streams. They represent the high and low reported values, and are industry typical limit values.

1.2 Purity/Impurities/Additives

A polymerization inhibitor (typically tertiarybutylcatechol, CAS RN 98-29-3, at 50 ppm) is usually added to Crude Butadiene C4 streams prior to shipment.

1.3 Physico-Chemical Properties

The two streams in this category are complex, containing many different hydrocarbons (Table 2), and can vary in composition not only between manufacturers but also for an individual manufacturer, depending on feedstock type and operating conditions. The seven constituents listed in Tables 3 and 4 comprise significant proportions of the two streams, which is why they were selected to represent the potential range of physico-chemical (PC) properties of the streams in this category. Therefore, these data can be used to adequately characterize the five PC endpoints of substances in this category for the HPV Program.

Table 3. Summary of Calculated Physico-Chemical Properties for Selected Chemicals Contained by Streams in the Crude Butadiene C4 Category

Chemical	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (hPa@ 25°C)	Log P_{ow}	Water Solubility (mg/L)
Isobutane	-132.6	3.2	3.45 E3	2.23	496.4
n-Butane	-120.3	19.6	2.41 E3	2.31	424.1
Isobutylene	-130.9	10.2	2.97 E3	2.23	495.6
cis-Butene-2	-120.4	27.8	2.31 E3	2.09	652.7
trans-Butene-2	-120.4	27.8	2.31 E3	2.09	652.7
Butene-1	-121.7	17.6	2.48 E3	2.17	557.7
1,3-Butadiene	-123.2	15.6	2.73 E3	2.03	732.4

Calculated values derived by the EPIWIN program (EPIWIN, 1999).

Table 4. Summary of Measured Physico-Chemical Properties for Selected Chemicals Contained by Streams in the Crude Butadiene C4 Category

Chemical	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (hPa@ 25°C)	Log P_{ow}	Water Solubility (mg/L)
Isobutane	-138.3	-11.7	3.08 E3	2.76	175.1
n-Butane	-138.2	-0.5	2.43 E3	2.89	135.6
Isobutylene	-140.4	-6.9	3.08 E3	2.34	399.2
cis-Butene-2	-105.5	0.8	2.33 E3	2.31	423.5
trans-Butene-2	-105.5	0.8	2.33 E3	2.33	407.1
Butene-1	-145.0	-1.3	3.00 E3	2.40	354.8
1,3-Butadiene	-108.9	-4.4	2.81 E3	1.99	792.3

Measured values from the EPIWIN experimental database (EPIWIN, 1999).

The following sections identify the values used to define the five PC endpoints of the two streams in this category.

1.3.1 Melting Point (Range)

Based on calculated values, the streams in this category can have a melting point range of -132.6 to -120.3 °C. Based on measured values, the streams in this category can have a melting point range of -145.0 to -105.5 °C. The calculated data compare favorably with the measured data. The measured data are considered the appropriate primary data set to characterize the melting point range of category members.

1.3.2 Boiling Point (Range)

Based on calculated values, the streams in this category can have a boiling point range of 3.2 to 27.8 °C. Based on measured values, the streams in this category can have a boiling point range of

-11.7 to 0.8 °C. The calculated data are not comparable with the measured data. The measured data are consistent with process knowledge and are considered the appropriate primary data set to characterize the boiling point range of category members.

1.3.3 Vapor Pressure (Range)

Based on calculated values, the streams in this category can have a vapor pressure range of 2.31 E3 to 3.45 E3 hPa at 25 °C. Based on measured values, the streams in this category can have a vapor pressure range of 2.33 E3 to 3.08 E3 hPa at 25 °C. The calculated data compare favorably with the measured data. The measured data are consistent with process knowledge and are considered the appropriate primary data set to characterize the vapor pressure range of category members.

1.3.4 Log P_{ow} (Range)

Based on calculated values, the streams in this category can have a log P_{ow} range of 2.03 to 2.31. Based on measured values, the streams in this category can have a log P_{ow} range of 1.99 to 2.89. The calculated data compare favorably with the measured data for the unsaturated molecules, 2.03 to 2.23 vs. 1.99 to 2.40, respectively. In comparison, the calculated data for the saturated molecules are not comparable with the measured data. The measured data are considered the appropriate primary data set to characterize the log P_{ow} range of category members.

1.3.5 Water Solubility (Range)

Based on calculated values, the streams in this category can have a water solubility range of 424.1 to 732.4 mg/L. Based on measured values, the streams in this category can have a water solubility range of 135.6 to 792.3 mg/L. As with the log P_{ow} data, the calculated data compare favorably with the measured data for the unsaturated molecules, 495.6 to 732.4 mg/L vs. 354.8 to 792.3 mg/L, respectively. In comparison, the calculated data for the saturated molecules are not comparable with the measured data. The measured data are considered the appropriate primary data set to characterize the water solubility range of category members.

1.4 Category Justification

Much of the data used to characterize human health endpoints of the two streams in the Crude Butadiene C4 Category are for 1,3-butadiene, which is the most chemically reactive of the constituents and hence presumed the most biologically active component and major contributor to toxicological activity. This chemical is present in the streams covered by this category at concentrations between approximately 10 to 92% (by weight). The presence of this chemical at concentrations $\geq$10% by weight presupposes that the stream would result in positive genotoxicity as the most sensitive endpoint. Supporting this presumption, two C4 Crude Butadiene stream samples, each with a different % 1,3-butadiene concentration (10 and 45%), have been shown to be genotoxic in mice.

At the time of this document's preparation, 1,3-butadiene has adequate quality data to characterize each HPV Program human health endpoint. Although an older acute inhalation toxicity study contained insufficient experimental detail to fully assess its quality, the results are consistent with the overall understanding of the hazard for this chemical. Therefore, the existing study was used to characterize the acute toxicity endpoint for 1,3-butadiene and to support the characterizaton of this category as a whole. There are also test data available for three different samples from the C4 Crude Butadiene stream. The composition of these samples was:

- 67% 1,3-butadiene; 30% butenes; 2% 1,2-butadiene; 1% other
- 45% 1,3-butadiene; 20% butanes; 30% butenes; 5% other

- 10% 1,3-butadiene; 29% 1-butene; 29% trans-2-butene; 12% cis-2-butene; 11% isobutylene; 4% n-butane; 4% isobutane; 1% other

Data for pure 1,3-butadiene together with data from two mid 1,3-butadiene-content C4 Crude Butadiene stream samples (approximately 45 and 67%) and one low 1,3-butadiene-content C4 Crude Butadiene stream sample (approximately 10%), adequately characterize the HPV Program human health effects endpoints for the two streams in this category.

2 EXPOSURE AND USE

The Crude Butadiene C4 Category contains 10 CAS RNs (Table 1) that are associated with the following two process streams:

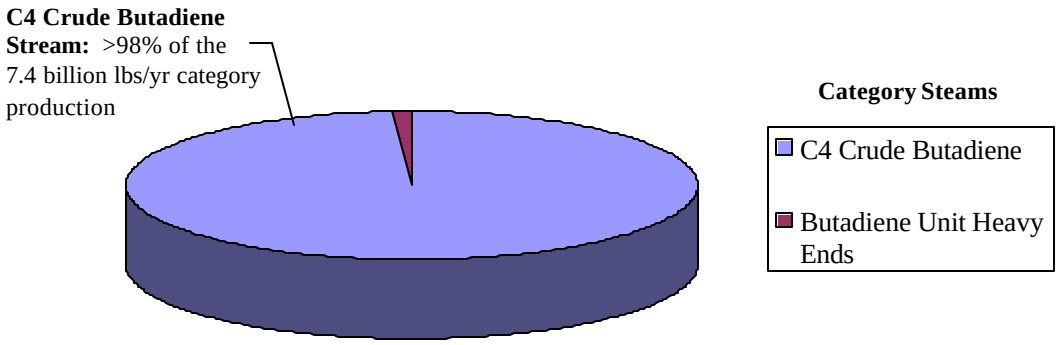
- C4 Crude Butadiene (referred to as Butadiene Concentrate in the Crude Butadiene C4 Category Test Plan)
- Butadiene Unit Heavy Ends (referred to as High Butadiene Heavy Ends in the Crude Butadiene C4 Category Test Plan)

These two streams are manufactured in ethylene production or butadiene finishing units (see Appendix II) and account for 100% of annual Crude Butadiene C4 Category production in the United States.

The C4 Crude Butadiene stream is a co-product of the ethylene manufacturing process and is processed at butadiene finishing units where it is separated into 1,3-butadiene and other 4-carbon (C4) chemicals. This stream accounts for over 98% of the 7.4 billion lbs/year (Figure 1), which was the total commercial production of streams in the Crude Butadiene C4 Category as reported by participants in the HPV Program based on their 1998 TSCA IUR reports. The balance of the category production consists of the Butadiene Unit Heavy Ends stream, which is recycled back into the production process or used as fuel in process furnaces. Subsequent processing of the streams in this category produces other substances (e.g., 1,3-butadiene) and the consumption of the original streams.

This category contains two Olefins Industry HPV streams that contain significant levels of 1,3-Butadiene (generally 10% by weight or greater). The C4 Crude Butadiene stream is transported in bulk by pipeline, barge, tank rail car, and infrequently by tank truck. There are no consumer uses of these streams and consequently no consumer exposure is expected.

Figure 1. Crude Butadiene C4 Category Production by Stream



For workers at ethylene and butadiene production plants where the streams in this category are manufactured and used, exposure to the streams is limited because processing occurs in closed systems. In addition, the Occupational Safety and Health Administration (OSHA) Butadiene Standard applies to these systems and thus limits worker exposure to the streams in this category. The Standard requires controls and work practices that limit 1,3-butadiene occupational exposure to less than 1 ppm, 8-hour TWA (time weighted average), and a short-term (15 minute) exposure of 5 ppm, which is the OSHA standard for 1,3-butadiene (OSHA, 1997). In addition, the OSHA Standard establishes an Action Level of 0.5 ppm (8-hour TWA), which effectively limits occupational exposure to 1,3-butadiene. Thus, the potential for occupational exposure to these streams is regarded to be minimal.

C4 Crude Butadiene, which accounts for approximately 98% of the production volume in the category, typically contains 50% 1,3-butadiene (reported concentrations of 1,3-butadiene in the C4 Crude Butadiene stream range from 10 to 82%). An 8-hour TWA and 15-minute STEL (Short Term Exposure Limit) occupational exposure to a typical C4 Crude Butadiene stream might approach 2 ppm and 10 ppm, respectively, for a facility complying with the OSHA 1,3-Butadiene Standard. Facilities that control below the Action Level of 0.5 ppm would have proportionally lower occupational exposures. For industrial workers at these facilities, the most likely exposure potential occurs through inhalation of low-level concentrations in air of vapors that escape from the closed process, such as fugitive emissions from valves and flanges; operations such as sampling, connecting, and disconnecting bulk transportation vessels (tank rail cars and barges); and during infrequent opening of equipment for maintenance.

Fugitive emissions and other emission sources can also result in the potential for low-level ambient air concentrations of the 2 category streams at locations neighboring the industrial facilities. Both EPA and state agencies enforce a wide range of volatile organic compound and hazardous air pollutant environmental regulations that control these emissions. Most industrial facilities (21 of 23 reporting sites) that produce or use these streams are located in the states of Texas or Louisiana. In Louisiana, the facilities are subject to an off-property 1,3-butadiene ambient air standard of 0.92 $\mu g/m^3$ (0.42 ppb) (Louisiana Department of Environmental Quality, 2003). Facilities in Texas are

subject to other requirements[1]. 1,3-Butadiene off-property concentrations resulting from category streams will be further reviewed nationally by EPA as the Clean Air Act Section 112f residual risk provisions are implemented. These regulations on 1,3-butadiene emissions limit the potential for emissions of the streams in this HPV Category.

Industrial emissions of chemicals such as 1,3-butadiene are reported annually to the EPA and made available to the public in the Toxics Release Inventory (TRI)[2]. The TRI is a publicly available EPA database that contains information on chemical releases and other waste management activities reported annually by selected industry groups as well as federal facilities. This inventory was established under the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) and expanded by the Pollution Prevention Act of 1990.

The TRI data indicate that industrial emissions of 1,3-butadiene have significantly decreased since 1988 as production increased. 1,3-Butadiene production increased from 3.17 billion pounds in 1988 to 4.43 billion pounds in 2000 (Chemical and Engineering News; 1998, 2002). The TRI data from 2000 indicate that emissions of 1,3-butadiene declined by 69% since 1988 or from 7.7 million pounds to 2.4 million pounds per year in 2000. Similarly, Louisiana and Texas, where most of the 1,3-butadiene reporting industrial facilities are located, reported similar decreases in 1,3-butadiene TRI emissions since 1988: 69% and 67%, respectively, for total emissions and 69% and 63%, respectively, for air emissions.

The EPA National Toxics Inventory (NTI)[3] includes reported emissions of 1,3-butadiene. Emissions from streams in the Crude Butadiene C4 Category make up a part of the chemical sector's contribution to the NTI. The NTI includes emissions from major sources (e.g., chemical plants and oil refineries), area sources (e.g., gas stations), other stationary sources (e.g., wildfires and other prescribed burning), and mobile sources. Mobile sources include both on-road and off-road sources of emissions (e.g., cars, trucks, buses, off road vehicles, aircraft, locomotives, and commercial marine vessels).

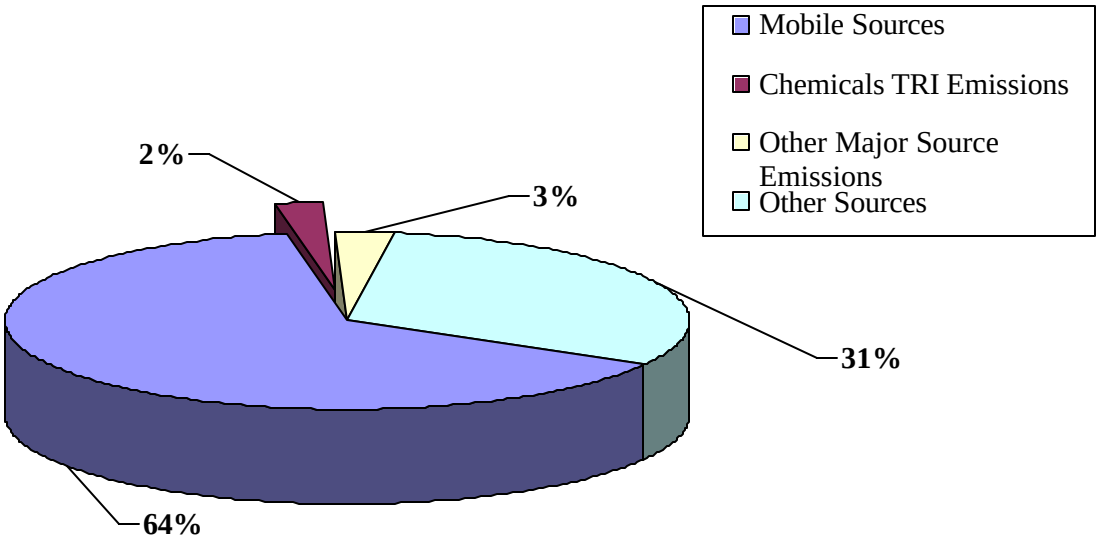
The 1996 NTI indicates total nationwide 1,3-butadiene emissions were 52,000 tons (104 million pounds). Major sources accounted for 5% of this total, mobile sources accounted for 64% and other sources made up the remaining 31%. The chemical sector's 1996 1,3-butadiene air emissions from the TRI data are a component of the NTI major source emissions, and equivalent to 2% of the total NTI emissions. These values are represented in Figure 2.

[1] 1,3-Butadiene monitoring data for Texas from the Community Air Toxics Monitoring Network can be found at: http://www.tnrcc.state.tx.us/air/monops/cat97/pdfs/97butadi13.pdf.

[2] EPA TRI website: http://www.epa.gov/tri/.

[3] Information concerning the EPA's NTI and their National Air Toxics Assessment can be found on the EPA Air Toxics website: http://www.epa.gov/ttn/atw/.

Figure 2. Percent 1,3-Butadiene Air Emissions by Source - 1996 Data



3 ENVIRONMENTAL FATE

3.1 Photodegradation

The atmosphere is the environmental compartment of interest when considering fate processes that can impact the persistence of streams in the Crude Butadiene C4 Category because they are gaseous. Results from an environmental distribution model support the assessment that chemical constituents of these streams will partition predominantly to the air compartment. The modelling results can be largely explained by the high vapor pressure of the constituents evaluated. In spite of their water solubility, wet deposition of category constituents is not likely to play a significant role in their atmospheric fate. Constituents of streams in this category have the potential to degrade at a significant rate in the atmosphere through indirect photolytic process mediated primarily by hydroxyl radicals (OH^-). In comparison, direct photolysis is not expected to contribute to the degradative fate of these streams in the aqueous environment.

3.1.1 Direct Photodegradation

The direct photolysis of an organic molecule occurs when it absorbs sufficient light energy to result in a structural transformation (Harris, 1982a). The reaction process is initiated when light energy at a specific wavelength elevates a molecule to an electronically excited state. However, the excited state is competitive with various deactivation processes that can result in the return of the molecule to a non excited state.

The absorption of light in the ultra violet (UV)-visible range, 110-750 nm, can result in the electronic excitation of an organic molecule. Light in this range contains energy of the same order of magnitude as covalent bond dissociation energies (Harris, 1982a). Higher wavelengths (e.g., infrared) result only in vibrational and rotational transitions, which do not tend to produce structural changes to a molecule.

The stratospheric ozone layer prevents UV light of less than 290 nm from reaching the earth's surface. Therefore, only light at wavelengths between 290 and 750 nm can result in photochemical

transformations in the environment (Harris, 1982a). Although the absorption of UV light in the 290-750 nm range is necessary, it is not always sufficient for a chemical to undergo photochemical degradation. Energy may be re-emitted from an excited molecule by mechanisms other than chemical transformation, resulting in no change to the parent molecule.

A conservative approach to estimating a photochemical degradation rate is to assume that degradation will occur in proportion to the amount of light at wavelengths >290 nm absorbed by the molecule (Zepp and Cline, 1977). Saturated hydrocarbons do not absorb light above 200 nm. Characteristic absorbance maxima (λ_{max}) and associated molar absorptivities (ε) for two unsaturated hydrocarbons, including 1,3-butadiene, are listed in Table 5 (Harris, 1982a).

Table 5. Characteristic Absorbance Maxima (λ_{max}) and Associated Molar Absorptivities (ε) for Two Unsaturated Hydrocarbons from Streams in the Crude Butadiene C4 Category

Hydrocarbon	λ below 290 nm	
	λ_{max*}	ε
Ethylene	193	10,000
1,3-Butadiene	217	20,900

* Values developed in organic solvents and regarded as approximate absorption maxima in aqueous solution.

Olefins with one double bond, two conjugated double bonds, or multiple un-conjugated bonds, which constitute the majority of the chemicals in the Crude Butadiene C4 Category, do not absorb appreciable light energy above 290 nm. Streams in this category do not contain constituent molecules of significant concentration that will undergo direct photolysis. Therefore, this fate process will not contribute to a measurable degradative removal of chemical constituents in this category from the environment.

3.1.2 Indirect Photodegradation

In the environment, organic chemicals emitted into the troposphere are degraded by several important transformation processes. The dominant transformation process for most compounds is the daylight reaction with hydroxyl (OH^-) radicals (Atkinson, 1988; Atkinson, 1989). The rate at which an organic compound reacts with OH^- radicals is a direct measure of its atmospheric persistence (Meylan and Howard, 1993).

AOPWIN estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The rate constants estimated by the program are then used to calculate atmospheric half-lives for organic compounds based upon an average atmospheric concentration of hydroxyl radicals.

Since the reactions necessary for this degradative process only take place in the presence of sunlight, the atmospheric half-lives are normalized for a 12-hour day. The seven chemicals selected to represent the atmospheric half-life range of streams in this category are C4 hydrocarbons that are predominant among the 10 CAS RNs (Table 6).

Atmospheric oxidation as a result of hydroxyl radical attack can be a significant route of degradation for streams in this category. Based on calculated values, streams in this category can have an atmospheric half-life range of 1.9 to 52.6 hours as a result of indirect photolysis by hydroxyl radical attack.

Table 6. Hydroxyl Radical Photodegradation Half-life of Selected Chemicals from Streams in the Crude Butadiene C4 Category

Chemical	Calculated Half-Life* (hrs)	OH^- Rate Constant (cm^3/molecule -sec)
Isobutane	52.6	2.4 E-12
n-Butane	48.8	2.6 E-12
Isobutylene	2.5	51.7 E-12
Cis-Butene-2	2.3	56.7 E-12
Trans-Butene-2	3.0	64.3 E-12
Butene-1	4.7	27.4 E-12
1,3-Butadiene	1.9	66.6 E-12

* Atmospheric half-life values are based on a 12-hr day and an OH^- concentration of 1.5E6, which is the default concentration used by the model.

3.2 Stability in Water (Hydrolysis)

Hydrolysis of an organic molecule occurs when a molecule (R-X) reacts with water (H_2O) to form a new carbon-oxygen bond after the carbon-X bond is cleaved (Gould, 1959; Harris, 1982b). Mechanistically, this reaction is referred to as a nucleophilic substitution reaction, where X is the leaving group being replaced by the incoming nucleophilic oxygen from the water molecule. The leaving group, X, must be a molecule other than carbon because for hydrolysis to occur, the R-X bond cannot be a carbon-carbon bond.

The carbon atom lacks sufficient electronegativity to be a good leaving group and carbon-carbon bonds are too stable (high bond energy) to be cleaved by nucleophilic substitution. Thus, hydrocarbons, including alkenes, are not subject to hydrolysis (Harris, 1982b) and this fate process will not contribute to the degradative loss of chemical constituents in this category from the environment.

Under strongly acidic conditions the carbon-carbon double bond found in alkenes, such as those in the Crude Butadiene C4 Category, will react with water by an addition reaction mechanism (Gould, 1959). The reaction product is an alcohol. This reaction is not considered to be hydrolysis because the carbon-carbon linkage is not cleaved and because the reaction is freely reversible (Harris, 1982b).

Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Neely, 1985). The chemicals in this category are primarily olefins that contain at least one double bond (alkenes). The majority of the remaining chemicals are saturated hydrocarbons (alkanes). These two groups of chemicals contain only carbon and hydrogen. As such, their molecular structure is not subject to the hydrolytic mechanism described above. Therefore, chemicals in the Crude Butadiene C4 Category have a very low potential to hydrolyze, and this degradative process will not contribute to their removal in the environment.

3.3 Distribution in the Environment

Fugacity-based multimedia modeling provides basic information on the relative distribution of a chemical between selected environmental compartments, which can include air, soil, water, sediment, suspended sediment, and biota. A widely used fugacity model, the EQC (Equilibrium Criterion) Level I model (Mackay *et al.*, 1996; Mackay, 1998) calculates chemical distribution between these compartments based on the input of basic physicochemical parameters including

molecular weight, water solubility, log P_{ow}, and melting point.

Results of the EQC Level I model (Table 7) for selected chemical constituents of streams from this category suggest that they will partition primarily to air, with a small percentage partitioning to water. These results can be explained by their high vapor pressure. Distribution of these chemicals to each remaining compartment (soil, sediment, suspended sediment, biota) is calculated as less than 0.01%.

The seven chemicals selected to characterize the transport/distribution range are C4 hydrocarbons that are predominant across the streams in this category. Physical property data (Table 4) used in the model are from the EPIWIN (1999) database.

Table 7. Environmental Distribution as Calculated by the EQC Level I Fugacity Model for Selected Chemicals from Streams in the Crude Butadiene C4 Category

Chemical	Distribution Per Environmental Compartment (%)					
	Air	Water	Soil	Sediment	Suspended Sediment	Biota
Isobutane	99.99	0.01	<0.01	<0.01	<0.01	<0.01
n-Butane	99.99	0.01	<0.01	<0.01	<0.01	<0.01
Isobutylene	99.99	0.01	<0.01	<0.01	<0.01	<0.01
cis-Butene-2	99.98	0.02	<0.01	<0.01	<0.01	<0.01
trans-Butene-2	99.98	0.02	<0.01	<0.01	<0.01	<0.01
Butene-1	99.99	0.01	<0.01	<0.01	<0.01	<0.01
1,3-Butadiene	99.97	0.03	<0.01	<0.01	<0.01	<0.01

Note: The distribution values were determined using physical property data from the EPIWIN (1999) database.

3.4 Biodegradation

Biodegradation is the use of a chemical by microorganisms as a source of energy and carbon. The parent chemical is broken down to simpler, smaller chemicals, which can be eventually converted to inorganic forms such as carbon dioxide, nitrate, sulfate, and water, depending on the composition of the parent chemical.

The microbial metabolism of aliphatic alkenes can be initiated by attack at the double bond (Watkinson and Morgan, 1990). Four degradative processes have been identified:

- Oxygenase attack upon a terminal methyl group to the corresponding alcohol, aldehyde, and acid
- Subterminal carbon oxygenase attack to the corresponding alcohol and ketone
- Oxidation across the double bond to the corresponding epoxide
- Oxidation across the double bond to the corresponding diol

Streams in the Crude Butadiene C4 Category are gaseous hydrocarbons, composed predominantly of chemicals with carbon numbers smaller than C5.

Constituent chemicals from the two process streams in this category are simple hydrocarbons (Table 2), the majority of which are calculated to partition primarily to the air where physical processes will contribute to their rapid degradation (see Indirect Photodegradation above for specific degradation rates of selected chemicals from this category). Consequently, their availability to microbial degraders can be significantly limited. Because of the partitioning behavior of

chemicals in this category, biodegradative processes will be less likely to contribute to their loss from the environment.

Streams from the Crude Butadiene C4 Category do not lend themselves to being evaluated for biodegradability using standard experimental designs because of their physical state. However, there is microbial metabolism information for several of the unsaturated C4 constituents in this category, including 1,3-butadiene, that demonstrates they have the potential to biodegrade. The sections immediately below summarize results of studies for selected constituents from this category. The data do not allow for an estimation of the extent of biodegradability relative to a standard 28-day test procedure using a microbial inoculum from a wastewater treatment facility. However, the constituents discussed below are predicted by BIOWIN, Biodegradation Probability Program (EPIWIN, 1999), as having the potential to biodegrade rapidly. [BIOWIN is a model in EPIWIN that calculates the probability of an organic chemical to rapidly biodegrade by a mixed population of microorganisms. BIOWIN can also estimate the time required to meet primary and ultimate biodegradation criteria.]

3.4.1 Propylene Biodegradation

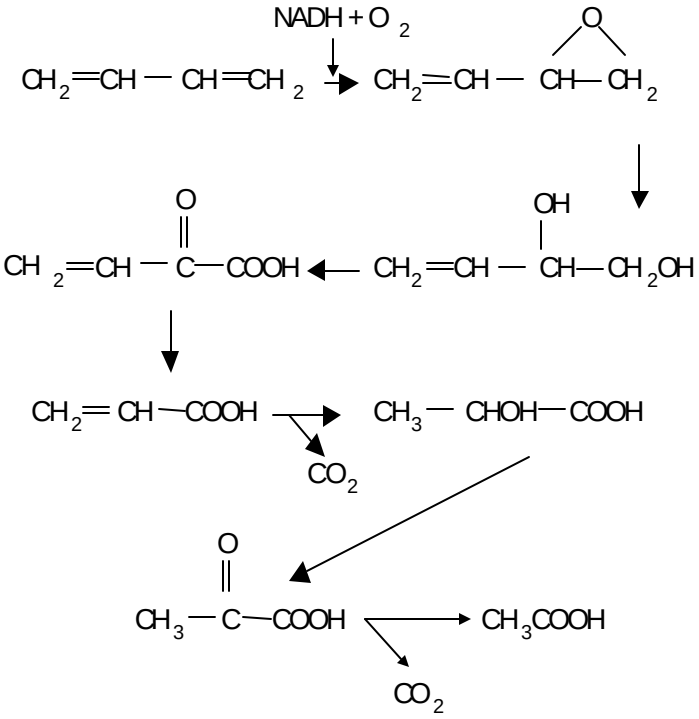
Propylene has been shown to be a growth substrate for several microorganisms. Isolated bacterial strains studied for their potential to biodegrade propylene under aerobic conditions were identified from the genus *Nocardia*, *Mycobacterium*, and *Xanthobacter* (de Bont *et al.*, 1980; de Bont *et al.*, 1982; de Bont *et al.*, 1983; van Ginkel and de Bont, 1986). Other species from the genus *Pseudomonas* and *Aerobacter* that were isolated from soil have also been associated with the ability to aerobically degrade propylene after they were shown to metabolize propylene oxide (Raja, 1991), an intermediate in the propylene metabolic pathway (van Agteren *et al.*, 1998).

Two pathways for the aerobic metabolism of propylene have been described (van Agteren *et al.*, 1998) that include the formation of either 1,2-propanediol or acetyl CoA prior to mineralization to CO_2.

3.4.2 1,3-Butadiene Biodegradation

Experimental studies to determine a catabolic pathway for 1,3-butadiene as mediated by a *Nocardia sp*. (Watkinson and Somerville, 1976) resulted in the series of reactions shown in Figure 3.

Figure 3. Proposed Microbial Metabolic Pathway for the Degradation of 1,3-Butadiene by a *Nocardia sp.*



The intermediary metabolic steps depicted in Figure 3 result in the production of acetic acid (CH_3COOH) which can be further metabolized. In addition, 1,3-butadiene has been estimated to have an aerobic aquatic biodegradation half-life ranging from 1 to 4 weeks (Howard *et al.,* 1991).

3.4.3 1-Butene Biodegradation

Isolated bacterial strains have been evaluated for their potential to biodegrade 1-butene under aerobic conditions. Bacteria from two genus, *Mycobacterium spp.* and *Xanthobacter spp.*, isolated from environmental samples have demonstrated the ability to degrade 1-butene (Hou *et al.*, 1983; Habets-Crützen *et al*., 1984; van Ginkel and de Bont, 1986; Weijers *et al*., 1995). Epoxybutane was shown to be converted to the corresponding ketone using a cell extract from a *Xanthobacter* spp. (Weijers *et al.*, 1995). These studies suggest that 1-butene can be biodegraded and that microbial metabolism can contribute to the overall loss of this chemical from the environment.

3.4.4 2-Butene Biodegradation

Although 2-butene has not been reported as a microbial growth substrate, an isolated bacterial strain, *Xanthobacter spp*., was evaluated for its potential to biodegrade various epoxyalkanes. Both diastereomeric forms of 2,3-expoxybutane were shown to degrade with degradation rates of 6 and 9 nmol/min/mg protein for trans- and cis- geometric isomers, respectively (Weijers *et al.*, 1988). These data suggest that a metabolic pathway is present in bacteria that will degrade these alkenes.

3.4.5 Isobutylene Biodegradation

Although isobutylene has not been reported as a growth substrate for bacteria, isolated bacterial strains have been evaluated for their potential to biodegrade 1-butene under aerobic conditions. Epoxybutane was shown to be converted to the corresponding ketone using a cell extract from a *Xanthobacter spp*.(Weijers *et al.*, 1995). In the same study, 2-methyl-1,2-epoxypropane was not converted suggesting that isobutylene metabolism is not mediated in a manner similar to 1-butene

by this organism. However, because of the structural similarity between 1-butene and isobutylene, isobutylene biodegradation may occur through a process not yet evaluated.

3.4.6 Abiotic and Biotic Degradation Summary

The stream constituents from this category will partition primarily to the air where physical degradative processes will dominate their fate. Data show that these chemicals are subject to rapid physical degradation. Selected constituents have also been shown to be subject to biodegradation. Overall, the constituent chemicals and consequently the streams from this category are expected to degrade rapidly in the environment from physical processes and not persist.

4 HUMAN HEALTH HAZARDS

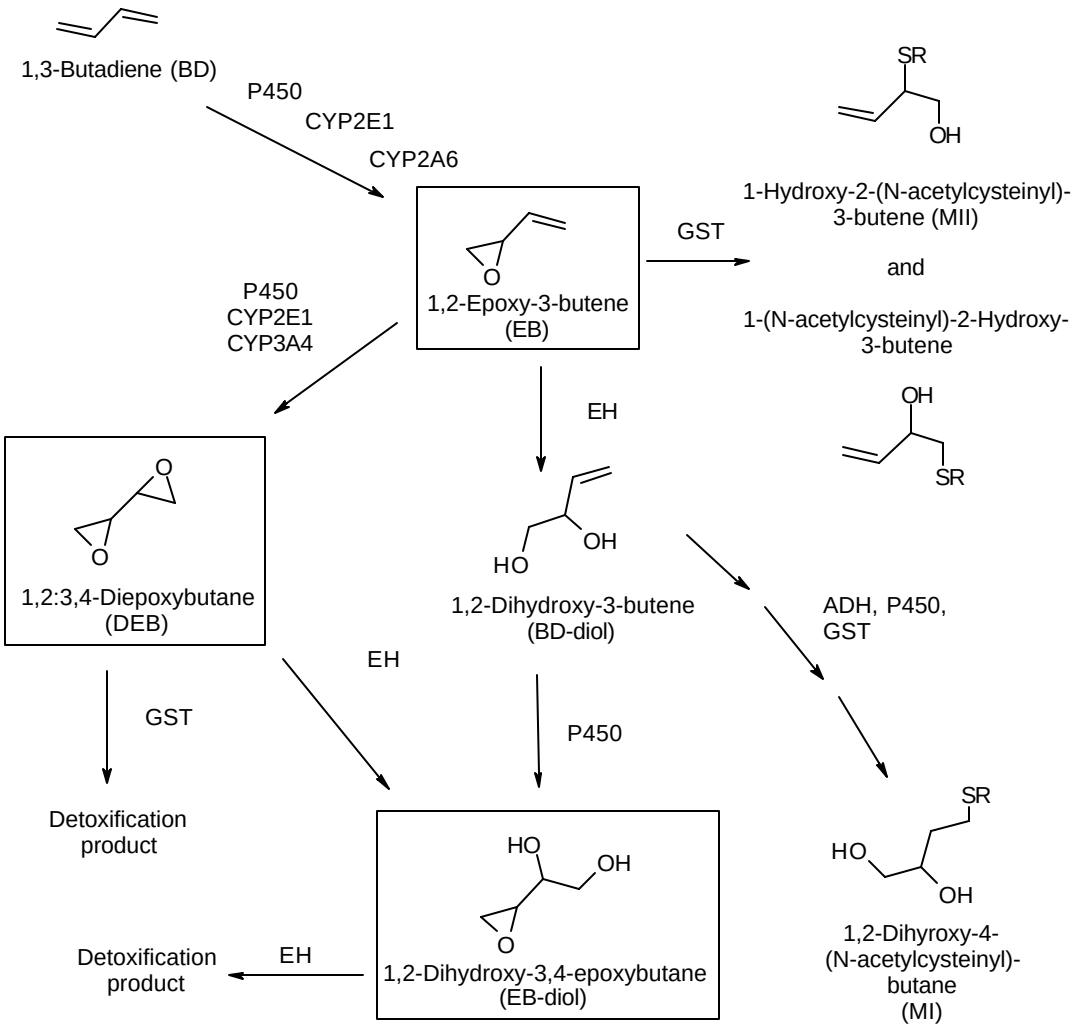
The two streams that comprise the Crude Butadiene C4 Category, which together contain ten CAS RNs, vary in 1,3-butadiene content, ranging from 10 to 92% 1,3-butadiene. Much of the data used to characterize the streams in this category are for 1,3-butadiene, which is the most biologically active constituent and thus the major contributor to toxicological activity. Therefore, data collected on 1,3-butadiene are included in the summaries below. The presence of this chemical at concentrations $\geq$10% by weight presupposes that the stream would result in positive genotoxicity as the most sensitive endpoint. Supporting this presumption, two samples from the Crude Butadiene C4 stream, containing 10 and 45% 1,3-butadiene, have been shown to be genotoxic. Data for pure 1,3-butadiene together with data from a mid 1,3-butadiene (approximately 45 to 67%) and a low 1,3-butadiene (approximately 10%) stream adequately characterize the HPV Program human health effects endpoints for the streams in this category.

4.1 Effects on Human Health

4.1.1 Toxicokinetics, Metabolism, and Distribution

1,3-Butadiene is initially oxidized to 1,2-epoxy-3-butene (EB), a reaction mediated primarily by P450 CYP 2E1 (Csanady *et al*., 1992; Duescher and Elfarra, 1994) (Figure 4). Further oxidation of EB produces 1,2:3,4-diepoxybutane (DEB) (Seaton *et al.*, 1995). Detoxification of EB proceeds by conjugation, mediated by glutathione-S-transferase (GST), or by hydrolysis, mediated by epoxide hydrolase (EH). Hydrolysis produces the 1,2-dihydroxy-3-butene (BD-diol) metabolite. Both DEB and BD-diol undergo further conversions *in vivo*, the former by EH mediated hydrolysis and the latter by P450 mediated oxidation, to produce the 1,2-dihydroxy-3,4-epoxybutane metabolite, known also as butadiene diol-epoxide (EB-diol) (reviewed in Himmelstein *et al.*, 1997). BD-diol can also be metabolized by P450 to hydroxymethylvinylketone (HMVK) (Kemper *et al.*, 1998), which may form $1N^2$-propanodeoxyguanosine DNA adducts *in vitro*. (Powley *et al*., 2003). EB, DEB, EB-diol, and HMVK are reactive electrophilic compounds with the potential to form carcinogenic intermediates from 1,3-butadiene metabolism *in vivo*.

Figure 4. Partial metabolic scheme for 1,3-butadiene (taken from Albertini *et al.*, 2003).



Direct GST mediated conjugation of EB with glutathione (GSH) leads to two detoxification products. One of these (i.e., 1-hydroxy-2-(N-acetylcysteinyl)-3-butene, also known as the urinary MII compound), as an isomeric mixture with 1-(N-acetylcysteinyl)-2-hydroxy-3-butene, is a biomarker of the conjugation detoxification pathway. GST mediated conjugation of HMVK with GSH leads to the production of 1,2-dihydroxy-4-(N-acetylcysteinyl)-butane (also known as the urinary MI compound). MI is a biomarker of the hydrolytic pathway because this detoxification pathway for EB is mediated initially by EH. The ratio MI/(MI + MII) in urine defines the relative importance of hydrolysis vs. conjugation in detoxification of EB (Bechtold *et al.*, 1994; reviewed in Henderson *et al.*, 1996).

In vitro studies have shown that mice are 2- and 10-fold more efficient than rats in oxidizing 1,3-butadiene to EB (Schmidt and Loeser, 1985; Csanady *et al.*, 1992). Furthermore, the second oxidation step to DEB could be mediated *in vitro* only by mouse liver microsomes (Csanady *et al.*, 1992). *In vivo* studies of 1,3-butadiene metabolism in mice and rats have also shown large inter-species differences. MI/(MI + MII) ratios in urine for mice and rats exposed to 1,3-butadiene by inhalation indicate that conjugation detoxification predominates in mice but that hydrolysis is more important in rats (Henderson *et al.*, 1996).

In summary, mice are more efficient in oxidation of 1,3-butadiene to electrophilic metabolites (especially to DEB), while rats are more efficient in hydrolytic detoxification. The existing metabolism data suggest that metabolism in humans appears to be more like metabolism in rats than in mice.

4.1.2 Acute Toxicity

Data are available to evaluate acute toxicity of streams in the Crude Butadiene C4 Category. As the streams are gaseous at room temperature, data are from inhalation toxicity studies (Table 8).

Table 8. Summary of Acute Inhalation Toxicity Data

CAS RN and Stream/Chemical Name (% 1,3-Butadiene)	Test Organism	Exposure Duration (hr)	LC_{50} (mg/m^3)
68955-28-2 C4 Crude Butadiene (45)	Rat	4	5,300
106-99-0 1,3-Butadiene (>99)	Rat	4	285,000
106-99-0 1,3-Butadiene (>99)	Mouse	2	270,000

Inhalation

Studies in Animals

Rats (5/sex) were exposed to 5,300 mg/m^3 of butadiene concentrate (CAS # 68955-28-2: 45% 1,3-butadiene; 20% butanes; and 30% butenes) in air for four hours (Gulf Oil Chemical Co., 1985). Clinical observations and body weights were recorded for fourteen days following exposure. No mortality was observed at this concentration and all rats appeared normal on days 2 to 14. Clinical observations included respiratory sounds in 2 male rats post exposure and minimal porphyrin around the eyes in one female rat. Necropsy revealed one female rat with an ovary filled with red fluid. The LC_{50} was >5,300 mg/m^3.

In a poorly reported study, LC_{50} values for 1,3-butadiene were determined to be 285,000 mg/m^3 (129,000 ppm) and 270,000 mg/m^3 (122,000 ppm) for rats (4 hr) and mice (2 hr), respectively (Shugaev, 1969).

Conclusion

Available data adequately address the acute toxicity of the Crude Butadiene C4 Category for the relevant route of inhalation exposure. Streams in this category are gaseous at room temperature. Acute inhalation toxicity tests have been conducted for streams containing either 45 or 100% 1,3-butadiene. No toxicity was observed for exposures up to 5,300 mg/m^3.

4.1.3 Irritation

Skin and eye irritation of Crude Butadiene C4 Category has been examined in rabbits.

Skin Irritation

Studies in Animals

In an irritation screening study, 0.1 ml of butadiene concentrate (CAS# 68955-28-2: 67% 1,3-butadiene; 30% butenes; and 2% 1,2-butadiene) was applied to the skin of one male and one female

New Zealand White rabbit (Mobil Environmental and Health Science Laboratory, 1985). The application site was occluded with a rubber dam. No irritation was observed at 1, 3, or 7 days after dosing.

Eye Irritation

Studies in Animals

In an irritation screening study, 0.1 ml of butadiene concentrate (CAS# 68955-28-2: 67% 1,3-butadiene; 30% butenes; and 2% 1,2-butadiene) was applied to the eye of one male and one female rabbit (Mobil Environmental and Health Science Laboratory, 1985a). Test stream was stored on dry ice prior to administration. No irritation was observed at 1, 3, or 7 days after dosing.

Conclusion

Butadiene concentrate is nonirritating to rabbit skin and eyes. Lack of irritation may be due to non irritating properties of the test stream or rapid removal of test stream from the application site by evaporation.

4.1.4 Repeated Dose Toxicity

Repeated dose toxicity tests have been conducted on a variety of streams in this category (Table 9). These studies range from 9 to 98 days in duration and have been conducted in rats and mice.

Table 9. Summary of Repeated Dose Toxicity Data

CAS RN and Stream Name (% 1,3-Butadiene)	Test Organism	Exposure Duration (days)	NOAEL (mg/m^3)
68476-52-8 C4 Crude Butadiene (10)	Crl:CD Rat	36	>20,000
106-99-0 1,3-Butadiene (>99)	CD Rat	91	>17,679
68955-28-2 C4 Crude Butadiene (45)	Fischer 344 Rat	9	>25,100
106-99-0 1,3-Butadiene (>99)	B6C3F1 Mouse	98	>2,760

Inhalation

Studies in Animals

Effects of repeated exposure to C4 Crude Butadiene (CAS# 68476-52-8: 10% 1,3-butadiene; 4% isobutane; 29% trans-2-butene; 29% 1-butene; 11% isobutylene; and 12% cis-2-butene) were evaluated as part of an OECD 422, Repeated Exposure Reproductive/Developmental Toxicity Screen in Crl:CD rats (Carney *et al.*, 2001). Twelve male and female rats were exposed to vapor concentrations 0; 2,000; 10,000; or 20,000 mg/m^3 Crude Butadiene for 36 or 37 days, 6 hr/da, 7 da/wk (this study contained an additional group of twelve female rats for reproductive and developmental toxicity screening evaluation). Males and females were sacrificed at the end of exposure. Effects on general toxicity, neurobehavioral activity, clinical chemistry, and hematology were evaluated. At necropsy, organs were weighed, evaluated grossly and histopathological evaluation was conducted. No deaths or treatment related clinical observations were reported. No treatment related changes were observed in body weight, sensory evaluation, rectal temperature,

fore/hindlimb grip performance, motor activity total counts, hematology, prothrombin time, clinical chemistry, organ weights, gross pathology, or histopathology. In evaluation of motor activity, the treatment-by-time by epoch interaction was significant. However, further evaluation indicated that this difference could be attributed to the time by epoch interaction rather than a treatment related effect. Females in the 2,000 mg/m^3 dose group had an increased hematocrit and a decrease in serum protein. However, these effects did not demonstrate a dose response and were not observed in males at the same dose level. As such these findings were considered incidental and not indicative of a treatment related response. The NOAEL in this study was 20,000 mg/m^3.

In a ninety-day repeat dose study, groups of 40 male and 40 female CD rats were exposed to 0; 2,209; 4,417; 8,334; or 17,679 mg/m^3 (0; 1,000; 2,000; 4,000; or 8,000 ppm, respectively) 1,3-butadiene (>99.2%, containing 120 ppm t-butyl catechol). Exposures were conducted for 6 hr/da, 5 da/wk for 13 weeks (Crouch *et al.*, 1979). Interim sacrifices of 10 rats/sex/group were conducted at 2 and 6 weeks, with blood being collected from all rats at these intervals and at terminal sacrifice. Body weights and food consumption were recorded weekly. Brain cholinesterase activity was determined in 5 rats/sex/group at the 2 and 6 week sacrifices and all rats at terminal sacrifice. Urine samples were collected from rats 1 to 2 weeks prior to sacrifice. Organ weights were determined for select organs with histopathology conducted on control and high exposure animals. Increased salivation was observed in female rats following 8 weeks of exposure. Decreased grooming was observed in male rats following ten weeks of exposure. Slight, non significant, reductions in body weight were observed in male rats. Organ weight and organ to brain weight ratios showed some scattered statistically significant differences among the groups but did not follow any consistent dose response trend. The NOAEL in this study was determined to be 17,679 mg/m^3.

No adverse effects were observed in rats following exposure to butadiene feedstock (CAS # 68955-28-2: 45% 1,3-butadiene; 20% butanes; and 30% butenes) in a well conducted short term repeated exposure study (Gulf Oil Chemicals Co., 1983a). Five male and five female Fischer 344 rats were exposed to 0; 2,500; or 25,100 mg/m^3 butadiene feedstock 6 hr/da, for a total of 9 days. Evaluations include body weight measurement, gross necropsy, organ weights, histopathology on selected organs, hematology, and clinical chemistry. With the exception of nasal discharge, no exposure related changes were observed. The NOAEL in this study was determined to be 25,100 mg/m^3.

Groups of 10 B6C3F1 mice/sex/group were exposed to 0; 1,380; 2,761; 5,522; 11,040; or 17,670 mg/m^3 (0; 625; 1,250; 2,500; 5,000; or 8,000 ppm, respectively) 1,3-butadiene (98.94% with 0.02% t-butyl catechol) 6 hr/da, 5 da/wk for 14 weeks (National Toxicology Program, 1984). Limited observations were conducted and included mortality and morbidity, body weight changes, gross pathology, and histolopathology on high dose and control animals. Mortality was observed in the 2,761 mg/m^3 group (1/10 males) and higher concentrations. Body weights were decreased at 5,522 mg/m^3 and higher concentrations. Despite mortality present at this concentration, the NOAEL was determined to be 2,761 mg/m^3.

Conclusion

Data are available to adequately characterize the repeated dose toxicity of Crude Butadiene C4 Category. The available studies were conducted by inhalation, the most appropriate route of exposure. Available studies cover a wide range of 1,3-butadiene concentrations (10 to 99%) in the test streams. The data are consistent in that they demonstrate minimal effects in rats with the exception of body weight changes following repeated inhalation exposures.

4.1.5 Mutagenicity

Genetic toxicity of crude butadiene has been evaluated both *in vitro* and *in vivo*. *In vitro* assays include Ames *Salmonella* Reverse Mutation assay, unscheduled DNA synthesis in rat hepatocytes, mammalian cell transformation assay, and mouse lymphoma assay. Potential for the *in vivo*

induction of chromosomal aberrations has been examined in rats and mice following inhalation exposure.

In vitro Studies

Studies in Animals

Mutagenic activity of 1,3-butadiene (CAS # 106-99-0) was evaluated in the Ames *Salmonella* Reverse Mutation assay (Arce *et al*., 1990). *Salmonella typhimurium* tester strains TA 97, TA 98, TA 100, and TA 1535 were overlaid on agar with or without mouse, rat, or human S9 activation systems in specially designed treatment chambers. 1,3-Butadiene gas was metered into the chambers at concentrations of 0, 30, 40, 50, and 60% for a 48-hour exposure period. An increase (just over 2-fold) in revertant colonies was observed only with the TA 1535 strain, all other strains demonstrated no increase. In this bacterial strain, mouse S9 had slightly higher activity than the uninduced rat or human S9 at 30% 1,3-butadiene in air. At concentrations greater than 30%, the number of revertants decreased in the presence of rat or human S9. Presence of human S9 did not substantially increase the number revertants compared to non S9 activated samples. Arochlor 1254 induced rat liver S9 fractions produced the same number of revertants as untreated mouse liver S9. Increasing the amount of rat S9 protein/plate slightly increased the number of revertants/plate without Arochlor 1254 induction, but did not produce an increase with Arochlor 1254 induction. In summary, 1,3-butadiene demonstrated weak mutagenic activity in this test system.

Butadiene concentrate (CAS # 68955-28-2: 67% 1,3-butadiene; 30% butenes; and 2% 1,2-butadiene) was evaluated for mutagenicity in the Ames *Salmonella* Reverse Mutation assay (Mobil Environmental and Health Sciences Laboratory, 1985b). Five strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537, and TA 1538) were incubated with 25, 50, 75, or 100 µl crude butadiene with and without Arochlor 1254 rat liver S9 activating system. Reversion frequencies in treated groups with and without S9 activation were similar to controls. The test stream was judged to be non mutagenic.

Butadiene concentrate (CAS# 68955-28-2: 45% 1,3-butadiene; 20% butanes; and 30% butenes), did not induce cell transformations in BALB/3T3-A31-1-1 cells treated *in vitro* with up to 20,000,000 mg/m^3 of the test stream (Gulf Oil Chemicals Co., 1983b). An increase in mutant frequency was observed in the mouse lymphoma cells following exposure to butadiene concentrate (CAS# 68955-28-2: 67% 1,3-butadiene; 30% butenes; and 1.2% 1,2-butadiene) in the absence of S9 activation. No increase was observed in the presence of S9 activating system (Mobil Environmental and Health Sciences Laboratory, 1985c). Unscheduled DNA synthesis (UDS) was observed in primary rat hepatocytes at 20,000,000 mg/m^3 butadiene concentrate (CAS# 68955-28-2: 45% 1,3-butadiene; 20% butanes; and 30% butenes), a level where marked cytotoxicity was observed (Gulf Oil Chemicals Co., 1984a) potentially confounding the data. No UDS was observed at treatment levels less than or equal to 10,000,000 mg/m^3.

In vivo Studies

Studies in Animals

Six male and female B6C3F1 mice were exposed to concentration of 500, 10,000, or 20,000 mg/m^3 C4 crude butadiene (CAS #, 68476-52-8: 10% 1,3-butadiene; 4% isobutane; 4% n-butane; 29% trans-2-butene; 29% 1-butene; 11% isobutylene; and 12% cis-2-butene) by inhalation for two days, 4 hr/day (Spencer *et al.*, 2001). Twenty-four hours following the final exposure, femoral bone marrow was collected to evaluate micronuclei formation in polychromatic erythrocytes. Cyclophosphamide was used as the positive control. Increases in the frequencies of micronuclei were observed in all groups treated with test material. Although a statistically significant dose

response was indicated, the difference between the low and high dose groups was minimal. Crude butadiene was positive for induction of micronuclei in this test system.

Twenty female CB6F1 mice and ten male Wistar rats were exposed to 0, 50, 200, or 500 ppm 1,3-butadiene for 5 days, 6 h/da by inhalation (Autio *et al.*, 1994). One day following exposure, smears of blood and bone marrow erythrocytes were prepared and stained. In rats, toxicity in bone marrow cells was observed in the 500 ppm exposure group. In rats, no increase in micronuclei frequencies were observed in either peripheral blood or bone marrow erythrocytes. In mice, a clear dose-dependent increase in micronuclei formation was observed in blood and bone marrow at all exposure levels tested.

Male and female Crl:CD-1 BR Swiss mice were exposed to 0; 10,780; 20,671; or 35,430 ppm butadiene concentrate (CAS # 68955-28-2: 45% 1,3-butadiene; 20% butanes; and 30% butenes) via inhalation for 2 hr/da for 2 consecutive days (Gulf Oil Chemicals Co., 1984b). Five mice per sex per dose were sacrificed on day 3 and day 4 (24 and 48 hours post-exposure), and bone marrow smears prepared. Loss of consciousness was observed in mice during exposures; no other adverse effects were observed. An increased incidence of micronuclei formation was observed at all dose levels on day three and at the two highest dose levels on day 4. Male mice exhibited an increase in micronuclei formation at the highest dose on both days.

Conclusion

Adequate data are available to evaluate the genotoxicity of crude butadiene C4. These data examine streams with a range of 1,3-butadiene content (10 to 99%). This range of 1,3-butadiene has been tested *in vitro* and *in vivo* test systems. *In vitro* studies indicate a weak mutagenic activity. *In vivo* studies demonstrate a genotoxic response from exposure to streams in this category.

4.1.6 Carcinogenicity

Inhalation

In vivo Studies in Animals

Male and female Sprague-Dawley rats were exposed to 0; 1,000; or 8,000 ppm 1,3-butadiene, 6 hr/day, 5 days/week for 111 weeks. Survival of both sexes was reduced at the high exposure level. An increase in incidence and number of animals with mammary tumors was observed in female rats at both the 1,000 and 8,000 ppm exposure levels. Increased incidences of thyroid gland adenomas and carcinomas, uterine sarcomas and Zymbal gland tumors were observed in female rats. The incidence of uterine sarcomas and Zymbal gland tumors were within the historical control range for these tumor types and may not have been related to treatment. An increased incidence in exocrine pancreas adenomas was observed in male rats at 8,000 ppm. An exposure related increase in Leydig cell tumors was observed in male rats at both concentrations.

Two cancer bioassays have been conducted in B6C3F1 mice. In the first study, male and female mice were exposed to concentrations of 0; 625; or 1,250 ppm butadiene for 61 weeks, at which time the study was canceled due to poor survivability (NTP, 1984). Numerous tumor sites were observed in both sexes. A dose-related increase in lymphomas, cardiac hemangiosarcomas and lung tumors was observed in both sexes. Increased incidence of papillomas or carcinomas of the forestomach, hepatocellular adenomas or carcinomas, ovarian granulosa cell tumors, acinar cell carcinomas of the mammary gland, brain gliomas, and Zymbal cell carcinomas were observed in one or both sexes.

Due to the poor survival rate in the initial study, a second study was conducted where B6C3F1 mice were exposed to 0, 6.25, 20, 62.5, 200 or 625 ppm 1,3-butadiene, 6 hrs/day, 5 days/week, for two years (NTP, 1993). Survival was reduced at exposure concentrations of 20 ppm and above. Tumors

were observed at numerous sites including lymphocytic lymphomas, histiocytic sarcomas, cardiac hemangiosarcomas, Harderian gland adenomas and carcinomas, hepatocellular adenomas and carcinomas, alveolar /bronchiolar adenomas and carcinomas, mammary gland adenoacanthomas and carcinomas, ovarian granulosa cell tumors and forestomach squamous cell papillomas and carcinomas. Alveolar/bronchiolar tumors were observed at the lowest dose administered in females (6.25 ppm).

Studies in Humans

Two large cohort studies provide the most definitive assessment of the relationship between cancer and butadiene exposure. One study was conducted on butadiene exposed workers in the synthetic rubber industry. Butadiene exposed workers in the butadiene monomer industry were evaluated in the second.

Delzell *et al.* (1996) evaluated mortality in a cohort of over 13,000 men employed at 8 different styrene-butadiene rubber (SBR) plants. The overall SMR for leukemia was 1.31 (95% CI = 0.97-1.74). Leukemia risks were concentrated among long-term workers with long latency working in jobs with the potential for high exposures to styrene and 1,3-butadiene. Greater than 2-fold increased leukemia risk occurred among hourly workers with more than 10 years employment and 20 years since hire and among workers in areas where there were potentially high exposures to 1,3-butadiene or styrene (e.g., polymerization, maintenance labor, laboratories). Overall about 75% of the cohort were exposed to 1,3-butadiene and 83% to styrene. In this same cohort of SBR workers, Delzell *et al.* (2001) evaluated the relationships between leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate (DMDTC). Past exposures to 1,3-butadiene, styrene and DMDTC were reconstructed through the use of exposure measurements and exposure modeling. In this analysis, leukemia mortality was significantly associated with cumulative 1,3-butadiene exposure, particularly for high ppm-years exposure levels. A stronger association was observed for cumulative 1,3-butadiene exposures with peak levels greater than 100 ppm. When concurrent exposure to styrene and DMDTC were considered, the effect of 1,3-butadiene exposure was reduced, but the exposure-response trend and apparent threshold remained. It was difficult to determine an independent effect of 1,3-butadiene exposure because of the high correlation of 1,3-butadiene exposure with styrene and DMDTC exposures. The strengths of this study are the large size, long follow-up and quantitative estimate of exposure. The weakness of this study is the concomitant exposures to styrene and DMDTC and uncertainty in the effects of 1,3-butadiene alone.

Divine and Hartman (2001) evaluated a cohort of almost 2,800 men employed at a 1,3-butadiene monomer producing plant. There were 18 cases of leukemia with an overall SMR of 1.29 (CI_{95} = 0.77 to 2.04) and all employed before 1950. The risk of leukemia decreased slightly among workers employed greater than 5 years compared to workers with less than 5-years employment in the high exposure group. This result was considered to be inconsistent with a dose-response effect. Over half the leukemia deaths occurred over 40-years since hire, which is considered an unusually long latency for leukemia. Cumulative 1,3-butadiene exposure was based on job exposure class, calendar time and length of time in job and was qualitative rather than quantitative as in the SBR study of Delzell *et al.* (2001). There was no suggestion of increasing risk with increasing 1,3-butadiene exposure. Because the exposure estimates were qualitative, it is not possible to determine the reasons for apparent absence of risk associated with 1,3-butadiene exposure in the monomer compared to the SBR study. It has been suggested that the lack of risk among monomer workers could be due to the absence of concomitant styrene and DMDTC exposures, or that 1,3-butadiene exposures were lower than the apparent threshold observed in the SBR study. The absence of risk among monomer workers is consistent with the lack of genotoxic effects among a small group of monomer workers from Prague (Albertini *et al.*, 2003). Biomarkers of exposure were related to 1,3-

butadiene exposure, but genotoxic effects were not related to 1,3-butadiene. Albertini *et al*. (2003) suggested that the lack of a genotoxic effect was not supportive of a cancer classification.

Conclusion

1,3-Butadiene is an animal carcinogen that demonstrates species differences in potency. 1,3-Butadiene is a potent, multi-site carcinogen in the mouse. Inhalation exposure to concentrations of 6.25 ppm produced lung tumors in B6C3F1 mice. Exposure to higher concentrations produced tumors at multiple sites. 1,3-Butadiene is a less potent carcinogen in rats. Although treatment related tumors were observed in the rat study, the potency and total tumor incidence was markedly different when compared to the mouse bioassays. The differences observed are likely due to the difference in 1,3-butadiene metabolism described in section 4.1.1.

Carcinogenic effects of 1,3-butadiene are more difficult to discern for humans. Epidemiology studies of workers exposed to 1,3-butadiene in the monomer industry demonstrated no increase in carcinogenic risk. In the synthetic rubber industry workers exposed to 1,3-butadiene demonstrated an increased risk of leukemia associated with long term exposure to high levels of 1,3-butadiene. The association was stronger when co-exposures to styrene and DMDTC were also considered. The difference in leukemia risk between these two groups could be related to differences in exposure to 1,3-butadiene, or the need for co-exposure to other agents in addition to 1,3-butadiene (styrene, DMDTC) for the expression of leukemia.

4.1.7 Toxicity for Reproduction

Several studies evaluated the reproductive and developmental toxicity of streams in the Crude Butadiene C4 Category (Tables 10 and 11). The streams evaluated ranged in 1,3-butadiene content from 10 to 100%. The majority of studies were conducted under standard protocols in compliance with GLP (good laboratory practices).

Table 10. Summary of Reproductive Toxicity Data

CAS RN and Stream Name (% 1,3-Butadiene)	Test Organism	OECD Test Guideline	NOAEL (mg/m^3)
68476-52-8 C4 Crude Butadiene (10)	Crl:CD Rat	422	>20,000 (Systemic) >20,000 (Reproductive)
106-99-0 1,3-Butadiene (>99)	Crl:CD Rat	421	>663 (Systemic) >13,260 (Reproductive)

Table 11. Summary of Developmental Toxicity Data

CAS RN and Stream Name (% 1,3-Butadiene)	Test Organism	OECD Test Guideline	NOAEL (mg/m^3)
68476-52-8 C4 Crude Butadiene (10)	Crl:CD Rat	422	>20,000 (Developmental) >20,000 (Maternal)
106-99-0 1,3-Butadiene (>99)	Crl:CD Rat	421	>13,260 (Developmental) >663 (Maternal)
106-99-0 1,3-Butadiene (>99)	CD Rat	414	>2,210 (Developmental) >442 (Maternal)
106-99-0 1,3-Butadiene (>99)	CD-1 Swiss Mice	414	>88.4 (Developmental) >88.4 (Maternal)

Effects on Fertility

Studies in Animals

Reproductive toxicity of C4 crude butadiene (CAS # 68476-52-8: 10% 1,3-butadiene; 4% isobutane; 4% n-butane; 29% trans-2-butene; 29% 1-butene; 11% isobutylene; and 12% cis-2-butene) was evaluated in an OECD 422 Repeat Dose Reproductive/Developmental Toxicity Screen (Carney *et al.*, 2001). Groups of 12 adult male and female Crl:CD Sprague-Dawley rats were exposed via inhalation to crude butadiene at concentrations of 0; 2,000; 10,000; or 20,000 mg/m^3, 6 hr/day, 7 days per week two weeks prior to breeding, during breeding, continuing to gestation day 19. Male rats were exposed for 36 to 37 days. No differences were observed in parental body weights, body weight gains or feed consumption between the groups. No treatment related effects were observed on mating, conception, fertility, or time to mating. Evaluations of gonadal function revealed no difference between treated and control groups. The NOAEL for reproductive toxicity was determined to be 20,000 mg/m^3.

Reproductive toxicity of 1,3-butadiene was evaluated in an OECD 421 inhalation reproduction and developmental toxicity screening test (WIL Research Laboratories, 2003). Adult male and female Crl:CD rats were exposed to concentrations of 0; 663; 3,313; or 13,260 mg/m^3 1,3-butadiene two week prior to breeding, during mating, gestation and lactation for a total of 83 to 84 consecutive days for F0 males, 60 to 70 total days for F0 females and 7 consecutive days for 2 groups of F1 offspring (one male and one female per litter on post natal days 21 to 27 or 28 to 34). In F0 and F1 animals a reduction in body weight was observed at 3,313 and 13,260 mg/m^3. Clinical signs of toxicity, chromodacryorrhea, chromorhinorrhea, and salivation in F0 animals as well as dried red material in the perioral and perinasal regions in the F1 pups were observed at 13,260 mg/m^3. No effect at any dose level was observed in any reproductive parameter examined including gonadal function, mating behavior, conception, gestation, parturition, and lactation. The systemic NOAEL for this study was 663 mg/m^3. The reproductive NOAEL was >13,260 mg/m^3.

The effect of 1,3-butadiene exposure on fertility in male mice was examined in a rodent dominant lethal test and sperm-head morphology assay (Morrissey, 1990). Male mice were exposed to 0; 442; 2,210; or 11,040 mg/m^3 1,3-butadiene via inhalation for 5 days, 6 hr/day. In the dominant lethal assay, CD-1 male mice were then mated to two unexposed female mice/week for eight consecutive weeks. In the two low dose groups slight differences were observed in ratio of dead to total implants, percentage of females with ≥2 dead implants and number of dead implants per pregnancy (also observed in the high dose group during week 1). No differences were observed in number of

pregnant females, implantations per litter, number of live fetuses, dead implantations/total implantations, or number of resorptions during weeks 1 and 2. No differences were observed for any endpoint during weeks 3 to 8. It was concluded, despite the lack of dose response, that 1,3-butadiene had an effect on mature germ cells. To assess sperm morphology, B6C3F1 mice were used and maintained for five weeks post exposure (Morrissey, 1990). At the end of the post exposure period, the reproductive tract was evaluated for gross lesions and sperm were obtained from the right cauda epididymus. A dose dependent increase in percentage of abnormal sperm was observed, becoming significantly different from control at the two highest exposure concentrations.

Developmental Toxicity

As part of an OECD 422 Repeat Dose Reproductive/Developmental Toxicity Screen (Carney *et al.*, 2001), no developmental toxicity was observed in Crl:CD Sprague-Dawley rats following exposure to C4 crude butadiene (CAS # 68476-52-8: 10% 1,3-butadiene; 4% isobutane; 4% n-butane; 29% trans-2-butene; 29% 1-butene; 11% isobutylene; and 12% cis-2-butene). Groups of 12 adult male and female rats were exposed via inhalation to crude butadiene at concentrations of 2, 10, or 20 mg/L (2,000; 10,000; or 20,000 mg/m^3), 6 hr/day, 7 days per week, 2 weeks prior to breeding, during breeding, and continuing to gestation day 19. No treatment related effects were observed in paternal body weights, body weight gains or feed consumption during the study. No difference was observed in number of viable litters, gestation length, litter size, pre implantation loss, pup body weight, or pup sex ratio. An increase was observed in post implantation loss in the low exposure group. This observation was considered spurious, given the lack of dose response. A single pup in the high dose group exhibited a hernia. This finding was considered spurious due to its low incidence. The NOAEL for this study was 20,000 mg/m^3.

A guideline OECD 414 developmental toxicity study was conducted in pregnant CD rats exposed to 0; 40; 200; or 1,000 ppm 1,3-butadiene on gestation days 6 to 15, 6 hr/day (Morrissey, 1990). Dams were sacrificed on gestation day 20. Decreased weight gain was observed in dams at 2,210 mg/m^3. There were no significant differences among the groups for number of live fetuses per litter, percent resorptions, malformations per litter, placental or fetal body weights or sex ratio. There was no evidence of developmental toxicity in any of the treated groups. The maternal NOAEL for this study was 442 mg/m^3 and the fetal NOAEL was 2,210 mg/m^3.

Developmental toxicity was evaluated in Crl:CD rats exposed to 0; 663; 3,313; or 13,260 mg/m^3 (0; 301; 1,507; or 6,006 ppm, respectively) 1,3-butadiene during the conduct of an OECD 421 inhalation reproduction and developmental toxicity screening test (WIL Research Laboratories, 2003). Adult male and female Crl:CD rats were exposed to 1,3-butadiene two week prior to breeding, during mating, gestation and lactation for a total of 83 to 84 consecutive days for F0 males, 60 to 70 total days for F0 females and 7 consecutive days for two groups of F1 offspring (one male and one female per litter on post natal days 21 to 27 or 28 to 34). In F1 offspring, a reduction in weight gain was observed in the 3,313 and 13,260 mg/m^3 groups during later stages of the lactation period. No indications of fetal toxicity or teratogenicity were observed. The systemic NOAEL for F0 and F1 animals was 663 mg/m^3. The developmental NOAEL was 13,260 mg/m^3.

Pregnant female CD-1 mice were exposed via inhalation to 0; 88.4; 442; or 2,210 mg/m^3 (0; 40; 200; or 1,000 ppm, respectively) 1,3-butadiene on day 6 to 15 of gestation, 6 hr/day using the OECD 414 developmental toxicity guideline (Morrissey, 1990). On day 18 of gestation, dams were sacrificed and maternal and fetal evaluations were made. Decreased maternal body weight gain was observed at 442 and 2,210 mg/m^3. Male and female fetal weights were reduced in the high dose groups. Placental weights were reduced for male fetuses at 200 ppm and males and females at 2,210 mg/m^3. Fetal variations (supernumary ribs and reduced sternebrae ossification) were increased in the 442 and 2,210 mg/m^3 groups. The maternal and developmental NOAEL for this study was 88.4 mg/m^3.

Conclusion

Effects on fertility and developmental toxicity of C4 Crude Butadiene (high butadiene concentration) are adequately defined with the available data. A stream with 1,3-butadiene concentration of approximately 10% produced no reproductive or developmental toxicity in rats exposed to concentrations as high as 20,000 mg/m^3. No reproductive or developmental toxicity was observed in rats exposed to concentrations up to 13,260 mg/m^3 1,3-butadiene. No developmental toxicity was observed in rats exposed to 2,210 mg/m^3 1,3-butadiene in the presence of maternal toxicity. These two streams cover the range of C4 Crude Butadiene streams (10% to approximately 100% 1,3-butadiene). As observed with other endpoints, mice are more susceptible than rats to developmental and reproductive toxicity of 1,3-butadiene, most likely due to an increased metabolic capacity in mice to form reactive metabolites. This is evident by the observation of developmental toxicity in mice at 442 mg/m^3 1,3-butadiene exposure. There is some indication of male mediated toxicity in mice following 1,3-butadiene exposure; however, the effect appears to be weak. As humans metabolize 1,3-butadiene in a manner more consistent with rats than mice, reproductive and developmental toxicity data developed in rats is more appropriate to use in assessing human risk.

The ability of 1,3-butadiene to cause ovarian atrophy is dependent on the production of the diepoxide metabolite and this differs between species (U.S. EPA, 2002). The mouse is the most sensitive species in terms of ovarian atrophy induction following 1,3-butadiene exposure while the rat is resistant to this effect. The observed species differences correlate with the production of the diepoxide metabolite of 1,3-butadiene, with the mouse producing higher levels of this toxic intermediate. Direct administration of the diepoxide metabolite of 1,3-butadiene can affect the rat ovary, albeit at higher dose levels than required for inducing similar effects in mice. Therefore, the mouse ovary is more sensitive to the toxic effects of both 1,3-butadiene and the diepoxide metabolite (U.S. EPA, 2002). Species differences in metabolism are explained in Section 4.1.1.

4.2 Assessment Summary for Human Health

Crude Butadiene C4 streams have a low order of acute toxicity. The components of Crude Butadiene C4 streams are gaseous at normal temperature and pressure; thus, ingestion or dermal absorption of this material is unlikely. Minimal effects were observed at concentrations of 5,300 mg/m^3.

Liquid Crude Butadiene C4 (test material was cooled in a dry ice bath) did not produce dermal or ocular irritation in rabbits. Exposure to liquid Crude Butadiene C4 is unlikely, as the components of the streams in this category are gases at normal temperature and pressure.

A species difference in repeated dose toxicity of Crude Butadiene C4 was apparent between rats and mice. Minimal effects were reported in rat repeated dose toxicity tests exposed to several Crude Butadiene C4 streams (1,3-butadiene content ranging from 10 to 99.2%). The no observable adverse effect levels were the highest concentrations tested or 17,679; 20,000; or 25,100 mg/m^3 (8,000; 9,060; or 11,365 ppm, respectively) following 90, 36, or 9 days or exposure, respectively. In contrast, mortality was observed in mice exposed to 2,761 mg/m^3 1,3-butadiene (99.2%) for 90 days. Well-documented species differences in 1,3-butadiene metabolism are the likely reason for the noted differences in repeat dose toxicity. Mice produce greater amounts of toxic metabolites following 1,3-butadiene exposure than rats. The existing metabolism data suggest that metabolism in humans appears to be more like metabolism in rats than in mice.

Test data demonstrate that Crude Butadiene C4 can produce genotoxicity. *In vitro*, Crude Butadiene C4 demonstrated little activity in reverse mutation assays conducted in *Salmonella typhimurium* either in the presence or absence of metabolic activation. In addition, Crude Butadiene C4 did not increase the number of transformed foci in C3H/10T1/2 clone 8 mouse embryo fibroblast cells. In the mouse lymphoma assay, evidence of mutagenic activity in mouse lymphoma L5178Y cells in

culture was observed in the absence of metabolic activation, but not in the presence of metabolic activation. *In vivo*, several Crude Butadiene C4 streams, containing 10 to 45% 1,3-butadiene, induced micronuclei formation in rats and mice following inhalation exposure.

Cancer data exist for 1,3-butadiene and these data are used as a surrogate for the Crude Butadiene C4 Category. Species differences exist in the carcinogenic response to 1,3-butadiene exposure. Similar to repeat dose data, mice are more sensitive than rats. Tumors are observed at lower exposure concentrations and at greater incidence than rats. In humans, an association between leukemia incidence and 1,3-butadiene exposure was observed in synthetic rubber workers exposed to 1,3-butadiene. The association was stronger when co-exposures to styrene and DMDTC were considered. No increase in leukemia incidence was observed in butadiene monomer workers.

No reproductive or developmental toxicity was observed in rats exposed to Crude Butadiene C4 during the conduct of an OECD 422 repeat dose reproductive/developmental toxicity screen. Exposures to concentrations of 20,000 mg/m^3 were without effect. Further, in a prenatal developmental toxicity study, inhalation exposure of pregnant rats to 1,3-butadiene on days 5 to 16 (inclusive) of gestation elicited no developmental toxicity at any tested concentration up to 2,210 mg/m^3. Maternal toxicity was observed at levels of 442 mg/m^3. Similar to observations of species differences in repeat dose toxicity, mice were more sensitive than rats in developmental and reproductive toxicity following exposure to 1,3-butadiene. This increased sensitivity was apparent in effects on male germ cells observed in a dominant lethal study and an assessment of sperm morphology in male mice and fetal effects observed in a prenatal developmental toxicity study. Chronic exposure to 1,3-butadiene increased the incidence of ovarian atrophy in mice, most likely related to the formation of butadiene diepoxide.

5 HAZARDS TO THE ENVIRONMENT

5.1 Aquatic Toxicity

The aquatic toxicity of streams in this category is expected to fall within a relatively narrow range regardless of their composition. This is expected because the constituent chemicals of these streams are neutral organic hydrocarbons whose toxic mode of action is non-polar narcosis (Ramos *et al.*, 1998). The toxic mechanism of short-term toxicity for these chemicals is disruption of biological membrane function (Van Wezel, 1995), and the differences between toxicities (i.e., LC/LL_{50}, EC/EL_{50}) can be explained by the differences between the target tissue-partitioning behavior of individual constituent chemicals (Verbruggen *et al.*, 2000).

The existing fish toxicity database for hydrophobic, neutral organic chemicals, which comprise the streams in this category, supports a critical body residue (CBR) for these chemicals between approximately 2-8 mmol/kg fish (wet weight) (McCarty *et al.*, 1991; McCarty and Mackay, 1993). The CBR is the internal concentration of a toxicant that causes mortality. When normalized to lipid content for most organisms, the CBR is approximately 50 µmol/g of lipid (Di Toro, 2000). Therefore, only hydrocarbon streams with components of sufficient water solubility, such that their molar sum in solution is high enough to produce a total partitioning to the organism of approximately 50 µmol of hydrocarbon per gram of lipid will demonstrate lethality.

Measured data are not available for the aquatic toxicity endpoints. However, structure-activity relationship (SAR) data developed with the ECOSAR model (Cash and Nabholz, 1999) were used to assess the aquatic toxicity for three trophic levels [the ECOSAR model used was from EPIWIN (1999)]. The ECOSAR model is a reliable and valid SAR model to apply to constituent chemicals from this category because it is based on a related chemical dataset that calculates the toxicity of neutral organic hydrocarbons whose toxic mode of action is non-polar narcosis. The calculated

aquatic toxicity values were determined using measured log P_{ow} values (ECOSAR requires selected physicochemical data and chemical structure to calculate effect concentrations).

Calculated aquatic toxicity values for chemicals representative of category members fall within a relatively narrow range. The effect range is a function of the range of log P_{ow} values identified for the chemicals. Streams in this category are expected to demonstrate 96-hour LC_{50} fish toxicity values in the range of 6.28 to 40.98 mg/L, 48-hour LC_{50} invertebrate toxicity values in the range of 7.15 to 43.88 mg/L, and 96-hour EC_{50} alga toxicity values in the range of 4.71 to 27.42 mg/L (Table 12).

Table 12. Summary of Aquatic Toxicity Data for Chemical Constituents in the Crude Butadiene C4 Category

Chemical Constituent (Log P_{ow}*)	Fish Toxicity 96-hour LC_{50} (mg/L)	Invertebrate Toxicity 48-hour EC_{50} (mg/L)	Alga Toxicity 96-hour EC_{50} (mg/L)
Isobutane (2.76)	8.32	9.39	6.13
n-Butane (2.89)	6.28	7.15	4.71
Isobutylene (2.34)	19.93	21.86	13.94
cis-Butene-2 (2.31)	21.26	23.28	14.81
trans-Butene-2 (2.33)	20.36	22.32	14.22
Butene-1 (2.40)	17.50	19.28	12.33
1,3-Butadiene (1.99)	40.98	43.88	27.42

* The log P_{ow} values used in the ECOSAR model are from the EPIWIN experimental database.

5.2 Assessment Summary for the Environment

Results of distribution modeling show that streams in the Crude Butadiene C4 Category will partition primarily to the air compartment, with a negligible amount partitioning to water. Although constituents have a moderate degree of water solubility, wet deposition of category constituents is not likely to play a significant role in their atmospheric fate because they rapidly photodegrade. Volatilization to the air will contribute to the rapid loss of category constituents from aqueous and terrestrial habitats. In the air, these constituents have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with calculated degradation half-lives ranging from 1.9 to 52.6 hours, depending on hydroxyl radical concentration. Aqueous photolysis and hydrolysis will not contribute to the transformation of category constituents in aquatic environments because they are either poorly or not susceptible to these reactions.

Although the biodegradability of streams in this category has not been evaluated with standard testing procedures because of their high volatility, studies have demonstrated that several category constituents can be degraded by bacteria isolated from soil and surface water samples. The results from these studies suggest that streams from this category are subject to microbial degradation. However, biodegradation is unlikely to contribute to the overall degradation of these streams because they tend to partition to the air compartment due to high volatility at ambient temperatures, and thus are less likely to be available to degrading microorganisms.

Due to the fact that streams in this category are gaseous at ambient temperature and pressure and expected to partition predominantly to the atmosphere, no aquatic toxicity testing was conducted. However, the ECOSAR model was used to predict aquatic toxicity using the equation for neutral organics, a reliable estimation method for this class of chemicals. Calculated acute toxicity values of selected category constituents for fish (96-hr) and invertebrates (48-hr) range from 6.28 to 40.98

mg/L and from 7.15 to 43.88 mg/L, respectively. For algae, the calculated 96-hr EC_{50} ranges from 4.71 to 27.42 mg/L.

6 DATA SUMMARY

Physico-chemical, environmental fate and effects, and human health data that characterize the two streams in the Crude Butadiene C4 Category are summarized in Tables 13 and 14. CAS RNs are associated with streams as follows:

- **C4 Crude Butadiene Stream**
  - 68476-52-8
  - 68187-60-0
  - 68955-28-2
  - 64742-83-2
  - 68476-44-8
  - 68956-54-7
  - 68477-41-8
  - 25167-67-3
- **Butadiene Unit Heavy Ends Stream**
  - 69103-05-5
  - 68477-41-8
  - 68512-91-4

Table 13. Physico-Chemical and Environmental Data Used to Characterize Streams and CAS RNs in the Crude Butadiene C4 Category (ranges are based on data for the most representative chemical subset for category streams and CAS RNs)

Endpoint	Crude Butadiene C4 Category Streams and CAS RNs								
							Butadiene Unit Heavy Ends Stream		
	C4 Crude Butadiene Stream								
	68955-28-2	68476-44-8	25167-67-3	68187-60-0	68476-52-8	68956-54-7	68477-41-8	68512-91-4	69103-05-5
Melting Point*/ Range (°C)	-145.0 to -105.5 (m)								
Boiling Point*/ Range (°C)	-11.7 to 0.8 (m)								
Vapor Pressure*/ Range (hPa)	2.33 E3 to 3.08 E3 (m)								
Log P_{ow}*/ Range	1.99 to 2.89 (m)								
Water Solubility*/ Range (mg/L)	135.6 to 792.3 (m)								
Direct Photodegradation	Direct photolysis will not contribute to degradation								
Indirect (OH-) Photodegradation* (half-life, hrs) (c)	1.9 to 52.6 (a)								
Hydrolysis	Hydrolysis will not contribute to degradation								
Distribution*	>99.9% partitions to air <0.1% partitions to water								
Biodegradation	Potential to biodegrade								
96-hr Fish Acute Toxicity* (mg/L)	22.03 to 37.59 (c)								
48-hr Invert Acute Toxicity* (mg/L)	24.11 to 40.27 (c)								
96-hr Alga Toxicity* (mg/L)	15.35 to 25.27 (c)								

* Constituent chemicals used to define selected endpoints include: isobutane; n-butane; isobutylene; cis-butene-2; trans-butene-2; butene-1; 1,3-butadiene
(m) Measured values (c) Calculated values (a) Atmospheric half-life values are based on a 12-hr day.

Table 14. Human Health Data Summary Used to Characterize Streams and CAS RNs in the Crude Butadiene C4 Category

Endpoint	Human Health Data Based on 1,3-Butadiene Content (wt%) for Crude Butadiene C4 Category Streams (CAS RNs)									
	10%	20	30	40	50	60	70	80	90	100
	C4 Crude Butadiene Stream (64742-83-2, 68955-28-2, 68476-44-8, 25167-67-3, 68187-60-0, 68476-52-8, 68956-54-7, 68477-41-8)									
	Butadiene Unit Heavy Ends Stream (68477-41-8, 68512-91-4, 69103-05-5)									
Acute Toxicity (rat)	LC50 >5,300 mg/m^3									LC50 =285,000 mg/m^3
Irritation						Non Irritating (eyes / skin)				
Repeat Dose Toxicity (rat)	NOAEL >20,000 mg/m^3			NOAEL >25,100 mg/m^3						NOAEL >17,679 mg/m^3
Mutagenicity Ames Assay						Negative				Weakly Positive
Mutagenicity Mouse Micronucleus	Positive			Positive						Positive
Reproductive Toxicity (rat)	NOAEL >20,000 mg/m^3									NOAEL >13,260 mg/m^3
Developmental Toxicity (rat)	NOAEL (M&F) >20,000 mg/m^3									NOAEL (M) >663 mg/m^3 NOAEL (F) >13,260 mg/m^3

M Male F Female

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APPENDIX I

ETHYLENE PROCESS DESCRIPTION

A. Ethylene Process

1. Steam Cracking

Steam cracking is the predominant process used to produce ethylene. Various hydrocarbon feedstocks are used in the production of ethylene by steam cracking, including ethane, propane, butane, and liquid petroleum fractions such as condensate, naphtha, and gas oils. The feedstocks are normally saturated hydrocarbons but may contain minor amounts of unsaturates. These feedstocks are charged to the coils of a cracking furnace. Heat is transferred through the metal walls of the coils to the feedstock from hot flue gas, which is generated by combustion of fuels in the furnace firebox. The outlet of the cracking coil is usually maintained at relatively low pressure in order to obtain good yields to the desired streams. Steam is also added to the coil and serves as a diluent to improve yields and to control coke formation. This step of the ethylene process is commonly referred to as "steam cracking" or simply "cracking" and the furnaces are frequently referred to as "crackers".

Subjecting the feedstocks to high temperatures in this manner results in the partial conversion of the feedstock to olefins. In the simplest example, feedstock ethane is partially converted to ethylene and hydrogen. Similarly, propane, butane, or the hydrocarbon compounds that are associated with the liquid feedstocks are also converted to ethylene. Other valuable hydrocarbon streams are also formed, including other olefins, diolefins, aromatics, paraffins, and lesser amounts of acetylenes. These other hydrocarbon streams include compounds with two or more carbon (C) atoms per molecule, i.e., C2, C3, C4, etc. Propane and propylene are examples of C3 hydrocarbons and benzene, hexene, and cyclohexane are a few examples of the C6 hydrocarbons.

2. Refinery Gas Separation

Ethylene and propylene are also produced by separation of these olefins streams, such as from the light ends product of a catalytic cracking process. This separation is similar to that used in steam crackers, and in some cases both refinery gas streams and steam cracking furnace effluents are combined and processed in a single finishing section. These refinery gas streams differ from cracked gas in that the refinery streams have a much narrower carbon number distribution, predominantly C2 and/or C3. Thus the finishing of these refinery gas streams yields primary ethylene and ethane, and/or propylene and propane.

B. Crude Butadiene C4 Streams from the Ethylene Process

The intermediate stream that exits the cracking furnaces (i.e., the furnace effluent) is forwarded to the finishing section of the ethylene plant. The furnace effluent is commonly referred to as "cracked gas" and consists of a mixture of hydrogen, methane, and various hydrocarbon compounds with two or more carbon atoms per molecule (C2+). The relative amount of each constituent in the cracked gas varies depending on what feedstocks are cracked and cracking process variables. Cracked gas may also contain relatively small concentrations of organic sulfur compounds that were present as impurities in the feedstock or were added to the feedstock to control coke formation. The cracked gas stream is cooled, compressed and then separated into the individual streams of the ethylene process. These streams can be sold commercially and/or put into further steps of the process to produce additional materials. In some ethylene processes, a liquid fuel oil stream is produced when the cracked gas is initially cooled. The ethylene process is a closed process and the streams are contained in pressure systems. (See Figure 4 for a pictorial representation of the ethylene manufacturing process.)

The final streams from the ethylene process include hydrogen, methane (frequently used as fuel), and the high purity chemicals, ethylene and propylene. Other streams from the ethylene process are

typically mixed streams that are isolated by distillation according to boiling point ranges. It is a subset of these mixed streams that make up streams in the Crude Butadiene C4 Category.

C. Crude Butadiene C4 Category Streams

1. C4 Crude Butadiene

The C4 Crude Butadiene stream (previously referred to as Butadiene Concentrate stream) is separated by distillation from the condensed portion of the cracked gas. Typically, C4 Crude Butadiene is a fairly narrow boiling range mixture consisting predominately of C4 hydrocarbons. C4 Crude Butadiene may also contain lesser amounts of C3 or lighter hydrocarbons and C5 and heavier hydrocarbons, because the separation technology is not perfect. The 1,3-butadiene content of these streams is typically 40 to 60%, but can range from approximately 10 to 82% (Table 2). C4 Crude Butadiene streams are sometimes produced in "on purpose" butadiene units using, for example, an oxydehydrogenation process.

2. Butadiene Unit Heavy Ends

Several different technologies are used to separate 1,3-butadiene from the C4 Crude Butadiene stream produced by the ethylene process. All of these technologies use a solvent to effect the separation.

In one technology, the C4 Crude Butadiene stream is fed to an extractive distillation (ED) column and a C4 mixture referred to as “raffinate” (i.e., C4 olefins and paraffins) is separated from the top of the distillate column. The bottom from the ED column consists of solvent rich in 1,3-butadiene and small amounts of other C4s. The rich solvent is fed to the solvent stripper where the 1,3-butadiene and other C4s are taken overhead (removed). The stripped, lean solvent is transferred from the bottom of the stripper back to the ED tower. The overhead of the stripper is condensed and fed to the rerun tower (or postfractionator) where high purity 1,3-butadiene is produced as the overhead. Bottoms of the rerun tower consist of the higher boiling constituents of C4 Crude Butadiene stream (e.g., 1,2-butadiene). The 1,3-butadiene content of streams in the Butadiene Unit Heavy Ends stream (previously referred to as High Butadiene Heavy Ends) covered by this test plan can range from 13 to 92% (Table 2).

3. Pyrolysis C3+ and Pyrolysis C4+

Butadiene concentrate sometimes consists of the entire C3+ or C4+ portion of the cracked gas stream (Pyrolysis C3+ and C4+ streams, previously referred to as Full Range Butadiene Concentrate stream). In this case, the carbon number distribution is between C3 and C12 or even higher. Normally the C4+ full-range 1,3-butadiene concentrate is split by distillation into two streams, a C4 Crude Butadiene stream, described above, and pyrolysis gasoline stream. The C3+ stream is separated into these two streams plus a C3 stream. The C3 stream (Propylene Streams Category) and pyrolysis gasoline (High Benzene Naphthas Category) are covered by separate categories sponsored by the Olefins Panel of the American Chemistry Council (Table 15). There are only two examples where these broad-range streams have been reported to have been isolated. In both cases, it was a result of a shutdown of process equipment and not the result of routine production conditions. The Pyrolysis C4+ stream was site limited and the Pyrolysis C3+ was not. The 1,3-butadiene content of Pyrolysis C3+ and Pyrolysis C4+ streams can range from 12 to 42% (Table 2). The Pyrolysis C3+ and Pyrolysis C4+ streams are discussed as a separate category.

4. 1,3-Butadiene

High purity 1,3-butadiene (99.5%+) is produced by separation from C4 crude butadiene produced by the ethylene process. This separation is accomplished by using a solvent process, either extraction or more typically extractive distillation. “On purpose” units also produce a small percentage of the commercially available 1,3-butadiene by dehydrogenation and subsequent separation.

Figure 5. Crude Butadiene C4 Process Streams Flow Diagram from the Ethylene Manufacturing Process Unit

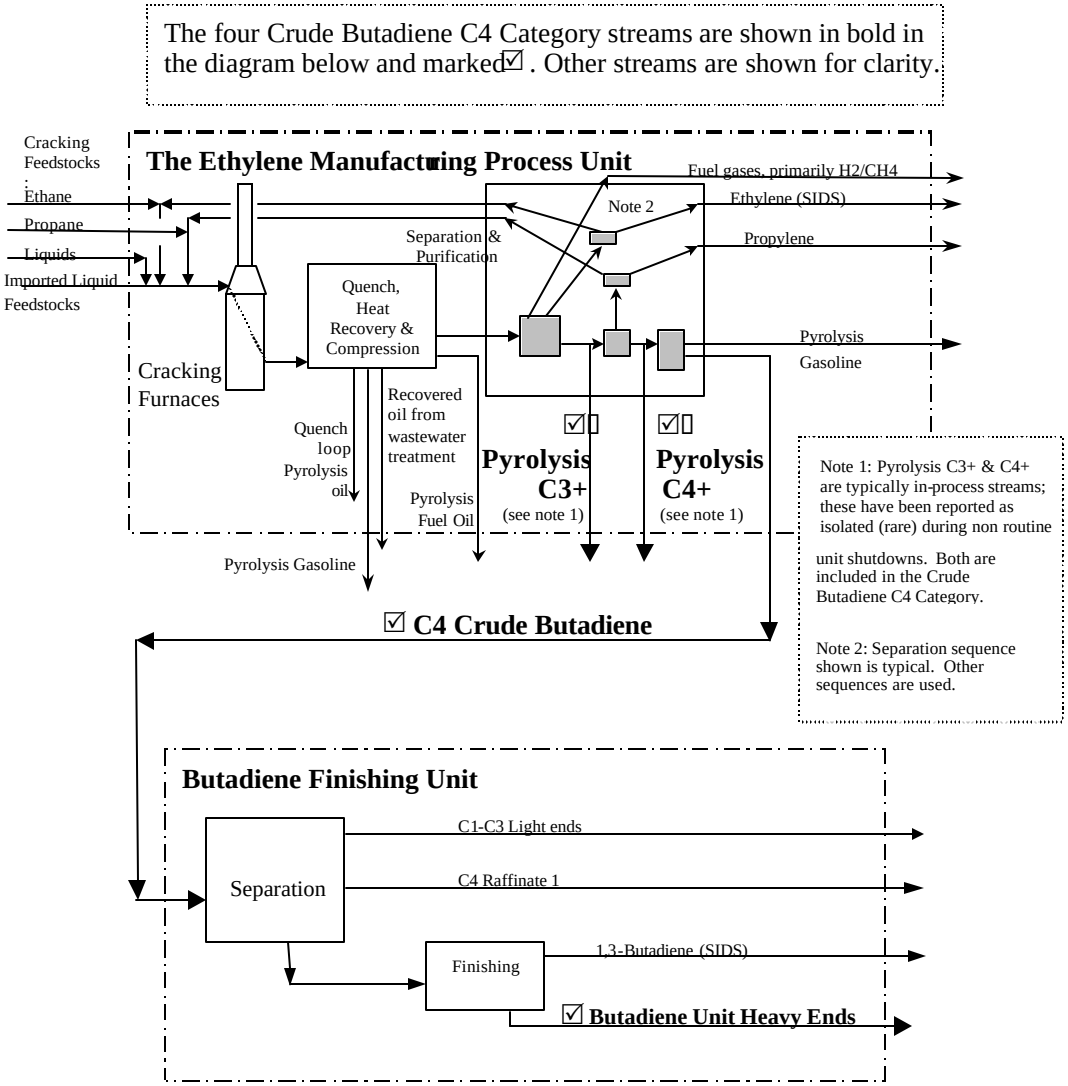

Table 15. HPV Program Categories Sponsored by the Olefins Panel of the American Chemistry Council

Category Number	Category Name
1	Crude Butadiene C4
2	Low 1,3-Butadiene C4
3	C5 Non-Cyclics
4	Propylene Streams
5	High Benzene Naphthas
6	Low Benzene Naphthas
7,8,9	Resin Oils & Cyclodiene Dimer Concentrates
10	Fuel Oils
11	Pyrolysis C3+ and Pyrolysis C4+